27+.

JEJUNOILEAL BYPASS

An experimental study in Zucker rats
and a retrospective study of morbidly obese patients

J. E. L. CREMERS

JEJUNOILEAL BYPASS

An experimental study in Zucker rats
and a retrospective study of morbidly obese patients

PROMOTORES

Prof. Dr. H. H. M. de Boer
Prof. Dr. U. J. G. van Haelst

JEJUNOILEAL BYPASS

An experimental study in Zucker rats
and a retrospective study of morbidly obese patients

PROEFSCHRIFT

ter verkrijging van de graad van doctor
in de geneeskunde
aan de Katholieke Universiteit te Nijmegen
op gezag van de Rector Magnificus
Prof. Dr. J. H. G. I. Giesbers
volgens besluit van het college van dekanen
in het openbaar te verdedigen op
donderdag 18 november 1982
des namiddags te 4 uur

door

Johannes Ernest Leonardus Cremers

geboren te Heerlerheide (Heerlen)

krips repro meppel

The studies presented in this thesis were performed in the Department of General Surgery (Prof. Dr. H.H.M. de Boer), University of Nijmegen; the Department of Pathology (Prof. Dr. H.P.M. Schillings, Prof. Dr. G.P. Vooys), University of Nijmegen; the Clinical Chemical Laboratory for Pediatrics and Surgery of St. Radboud's Hospital (Dr. P.J.J. van Munster), University of Nijmegen, and the Division of Experimental Microsurgery of the Central Animal Laboratory (Dr. W.J.I. van der Gulden), University of Nijmegen, The Netherlands.

Aan Hester,
Martje, Judith en Gineke,

Aan mijn ouders en Mia.

CONTENTS PAGE

Part 1 ANIMAL EXPERIMENT

Chapter 1

INTRODUCTION

1.1 History and types of intestinal bypass procedures

Obesity is a condition which has always been with mankind. However, the attitude towards overweight and obesity has changed from Greco-Roman times through the twentieth century (Ayers, 1958).
There has been a gradual shift away from acceptance, even idolatry,seen in the curvaceous nudes of Rubens's paintings,to rejection of obesity, as seen in the predominance of the very lean body types of most modern fashion models like "Twiggy" (Bray, 1976).
Apart from often being unable to work or enjoy life, the morbidly obese are predisposed to high bloodpressure, degenerative joint disease, diabetes and even sudden death. Without statistical evidence it was already known to William Shakespeare :
"Leave gourmandizing. Know the grave doth gape
For thee thrice wider than for other men."
(William Shakespeare, Henry IV, part II; Act V ,sc.V).
The heaviest man in world history is still alive. The American Jon Brower weighs 635 kg and needs 13 people to turn him in his bed.He is still aiming at a weight of 95 kg (Guinness Book of Records, 1981).
The literature credits Dr. Arnold J. Kremen and associates with the introduction of surgery for obesity (Kremen ,1954). Kremen and Linner were working on a research project under the guidance of Varco at the University of Minnesota, U.S.A. .
They compared bypass of the jejunum with bypass of the ileum in dogs with regard to prognosis and effect upon nitrogen absorption.
In the discussion of the paper by Kremen, Dr. Philip Sandblom of Lund, Sweden, referred to a Swedish surgeon, Dr. V. Henriksson of Gothenburg who " tried to control obesity in a woman whose appetite was better than her character", by resection of an appropriate amount of small intestine. He found that, "although the lady lost much weight, it was difficult to keep her in balance". The exact date was not given.
Kremen then mentioned his first 36-18 inches shunt, end-to-end, of a total small intestinal length of 164 inches, leaving the remaining small intestine within her peritoneal cavity.
Further investigation about Dr. Henriksson led me to Dr. J.G.Kral, who managed to track down two of Dr. Viktor Henriksson's original patients, two ladies in perfect health :
one in her eighties, the other 74 years old, both thin and enjoying perfect health (Personal communication, September 1981).
Dr. Henriksson's procedure consisted in resection of a large

part of the small intestine (Henriksson, 1952 and Kral, 1981). In 1963 Payne, De Wind and Commons reported a series of 9 patients in whom they had anastomosed 15 inches of jejunum to the transverse colon, thus bypassing part of the jejunum,the ileum, the colon ascendens and half of the transverse colon, as a "planned controlled intestinal bypass procedure".In the 10th patient 20 instead of 15 inches of jejunum were used (Payne,1963).
Their interest in intestinal bypass to bring about loss of weight had been stimulated by a patient, who steadily lost weight after undergoing massive small intestinal resection with anastomosis of the remaining proximal jejunum to the transverse colon.
Although loss of weight was achieved, severe diarrhea and electrolyte abnormalities ensued. Six of their patients had intestinal continuity reestablished after they had reached almost ideal weight. Nearly all these patients regained their preoperative weight.
One patient suddenly died of a pulmonary embolism after six months.
In three patients the jejuno-colic shunt was converted to a jejunoileal shunt.
In the first patient 15 inches of jejunum were anastomosed end-to-side to 10 inches of ileum, with good result: a weight of 123 pounds as compared to a preoperative weight of 268 pounds and a weight of 119 pounds after the jejuno-colic bypass. A satisfactory loss of weight was also seen in the second patient where 15 inches of jejunum end-to-side to 20 inches of functional ileum were left, resulting in values of 160, 243 and 118 pounds, respectively.
In the third patient 18 inches of jejunum were anastomosed end-to-side to 42 inches of ileum. This procedure did not induce any loss of weight since the postoperative value was 255 pounds as compared to a starting weight of 256 pounds. After jejuno-colic bypass weight had been reduced to 130 pounds.
To reduce the diarrhea and electrolyte complications, several surgeons increased the length of the jejunum to 20 or 25 inches (Sherman,1965; Lewis, 1966; Shibata, 1967).

Over 70 patients with a jejunocolic anastomosis have been reported in the medical journals (Payne et al.,1963; Wood and Chermos, 1963; De Muth and Rottenstein,1964; Sherman,1965; Lewis, Turnbull and Page,1966; Bondar and Pisesky, 1967; Kaufman and Weldon, 1967; Shibata, Mackenzie and Long, 1967; Maxwell, Richards and Albo, 1968; Shagrin et al. , 1971).
Loss of weight varied with lenght of jejunum. When 15 inches of jejunum were left, the patients lost 48 percent of their body weight in one year. When the upper intestinal segment was lengthened to 20 inches, patients lost 31 percent of their previous weight in 12 months. With 25 inches, loss of weight was even slower: 26 percent at 12 months (Shibata et al., 1967).
However, serious complications remained: severe electrolyte losses(Payne et al.,1963; De Muth,1964; Shibata, 1967),liver failure (Bondar,1967; Drenick, 1970), and at least 17 deaths

(Maxwell,1968).
Therefore, the elective jejuno-colic anastomosis in morbidly obese patients was abandoned and attention switched to jejunoileal bypass. Anastomosis between varying lengths of jejunum and ileum was investigated, e.g. 38 cm of jejunum + 20 cm of ileum, 35 cm of jejunum + 20 cm of ileum, 38 cm of jejunum + 15.5 cm of ileum, 38 cm of jejunum + 12,5 cm of ileum. In 1965 it was decided that 35 cm (14") of proximal jejunum anastomosed end-to-side to 10 cm (4") of distal ileum, was appropriate (Payne,1969).
In 1971 the following three papers were published which described end-to-end anastomoses between jejunum and ileum with the bypassed bowel anastomosed to the cecum, transverse colon, or sigmoid. This change was introduced because of unsatisfactory results and the idea that a variable degree of reflux into the bypassed ileum following end-to-side anastomoses caused unpredictability of loss of weight.
Buchwald and Varco (1971) were concerned with the combined problems of obesity and hyperlipidemia .
Since the terminal ileum is the site of greatest absorption of bile salts and cholesterol,they introduced an anastomosis,end-to-end, between 40 cm of jejunum and 4 cm of ileum. The bypassed bowel was connected to the cecum. This became their standard procedure for all morbidly obese patients.
Salmon (1971) compared in dogs jejuno-colic bypass anastomosing 60 centimetres of the proximal jejunum end-to-side to the transverse colon, jejunoileal bypass anastomosing 20 centimetres of the proximal jejunum end-to-side to the distal 40 centimetres of ileum, and jejunoileal bypass anastomosing 20 centimetres of the proximal jejunum end-to-end to the distal 40 centimetres of ileum. A fourth group was used for sham operation.
All dogs with jejuno-colic bypass died. Loss of weight initially occurred in the second and third group but after some time all dogs of group two regained their normal weight.
However, the dogs in group three, with the end-to-end anastomosis showed a consistent and sustained loss of weight.
As a result of these studies 120 morbidly obese patients were treated with an end-to-end jejunoileal bypass of 25 cm of jejunum to 51 cm of distal ileum.
It has to be mentioned that Salmon measured the bowel length on the antimesenteric border,which means that the total length of functioning bowel in his patients is probably comparable to that used by Buchwald, Scott and Payne on the mesenteric border (Mason,1981).
Scott et al.(1971) introduced their new technique as an end-to-end anastomosis of 30 cm of jejunum to 30 cm of ileum, draining the bypassed intestine into the transverse colon or sigmoid.
In 1973 Scott et al. compared 10 patients with a 30 cm to 30 cm jejunoileal bypass with 21 patients having a 30 cm to 15 cm jejunoileal end-to-end bypass.
The first group showed good results as regards bowel function, satisfactory nutritional and metabolic adaptation with minimal side effects, but did not achieve return to ideal weight status. In the second group the results appeared to be better

as to ideal weight status being achieved, but complications resulting from the procedure and side effects increased.
Danø et al.(1973) performed end-to-side anastomoses in 36 patients and varied the lengths of the segments from 12 to 24 to 36 cm but always kept the total length at 48 cm. Apart from a better vitamin B 12 absorption with 36 cm of ileum as compared to 12 cm of ileum, there was no significant difference between the three operations with respect to either loss of weight or complications.
Juhl et al.(1974) used end-to-side anastomosis of either 37 or 34 cm of jejunum to 13 cm of ileum. At 18 months the loss of weight was 36 kg and 61 kg , respectively, so 3 cm less meant a further loss of 25 kg.
Backman (1975) reported a significant correlation between loss of weight and initial weight.
Using an end-to-end anastomosis of 40 cm of jejunum to 4 cm of terminal ileum, with drainage of the bypassed bowel, end-to-side, into the cecum, Guzman et al. (1975) analyzed in 119 patients the correlation of certain variables with the achieved loss of weight. Statistically significant predictive variables, with a high correlation coefficient with the actual loss of weight (expressed as the percentage of ideal body weight) were preoperative weight and the intraoperative total small bowel length.
Backman and Hallberg (1975) compared end-to-side with end-to-end anastomosis using 40 cm of jejunum and 15 cm of ileum, and ileocecostomy for the draining of the bypassed intestine into the cecum.
Measurements of intestinal length were made midway between the mesenteric and the antimesenteric border. The final conclusion was that "if the rate of loss of weight is too fast the patient is in danger and if the rate is too slow the benefit of surgery is low". This conclusion was not influenced by the type of anastomosis used. Most complications,however, including electrolyte disturbance and liver insufficiency (nine patients, including three deaths), occurred in the 13 of 68 patients who had had end-to-end anastomosis.
Gaspar et al. (1976) compared the Payne procedure (35 cm of jejunum anastomosed end-to-side to 10 cm of ileum) and Scott procedure (30 cm of jejunum anastomosed end-to-end to 15 cm of ileum with the proximal cut end of ileum vented into the transverse colon) and found no advantage of one procedure over the other. Measurement was performed by stretching the mesenteric border of the intestine very tightly along a premeasured tape in two-inch to four-inch extensions.
To prevent regurgitation into the bypassed segment Payne et al. introduced a slight variation to the operation. They included an ileal jejunal suture line to sharpen the angle of the bypassed segment, thus eliminating regurgitation (Payne et al.1980).

1.2 Conclusion

A comparison between the procedures suggested by Payne and Scott (an end-to-side anastomosis between 35 cm of proximal jejunum and 10 cm of distal ileum versus an end-to-end anasto-

mosis between 30 cm of jejunum and 15 cm of ileum) reveals no decisive advantage in either of the two in their effects with respect to loss of weight and their complications.
With the Payne technique one anastomosis less needs to be made.
The total length of functioning small bowel appears critical in determining the weight-losing effect of the operation.
Since the gastric procedures for morbid obesity, gastric bypass and gastroplasty, and bilio-pancreatic bypass are beyond the scope of this thesis, they have not been included in this survey.

1.3 Aim of our study

The aim of the study was to find a suitable method and a suitable animal model to identify and possibly standardize the parameters which affect both rate and size of loss of weight and which cause some of the complications after jejunoileal bypass surgery.
Ultimately we wanted to look for correlations between the various parameters to examine if, under any conditions, loss of weight after jejunoileal bypass can be predicted from the length of the functional small intestine.
Since portacaval anastomosis is also known to cause loss of weight the effect of this shunt was evaluated and compared with jejunoileal bypass (Patricio, 1977).

ANIMAL MODEL

2.1 Experiments in animals

Several authors have changed both length and type of intestinal bypass because of dissatisfaction with their previous results (Section 1.1).
However, when we started our experiment early 1978, relatively few experiments in animals had been reported.
Bondar and Pisesky (1966) using 14 dogs and 1 pig, compared an 80% small intestinal resection with jejunoileal anastomosis,an 80% jejunoileal bypass,both end-to-end and end-to-side,and an 80% jejunocolic bypass.
Nygaard (1967,1968) compared end-to-end, side-to-side and end-to-side anastomoses in 50% and 70% resections, both proximal and distal of the small intestine, with 50% and 70% bypasses of proximal , middle and distal small intestine in the rat.
Mc.Clelland (1970) reported in mongrel dogs treated with end-to-side jejunoileal bypass that supplemental feeding by a jejunostomy had a positive effect in prevention of hepatic injury.
Salmon (1971) using dogs of different breed, studied 3 types of bypass : jejuno-colic, jejunoileal end-to-side (20 cm of jejunum and 40 cm of ileum) and jejunoileal end-to-end, all with 60 centimetres functional segments.
Armellini (1976), Baggio (1976) and Ottolenghi (1976) used Sprague-Dawley rats fattened with insulin and performed a jejunoileal bypass of 4 + 2 cm, which leaves 5% of functional small intestine.
Both O'Leary (1974) and Burney (1977) used mongrel dogs to study hepatic failure after jejunoileal bypass.
Madura (1975) and Grosfeld (1976,1977) introduced the Zucker rat as a new experimental jejunoileal bypass model and compared the effects of jejunoileal bypass (90%) in the Zucker rat with the results obtained with the Sprague-Dawley rat.
Hyland (1977) constructed a jejunoileal bypass of more than 90% in Wistar rats to compare abnormalities of liver functions with abnormalities of liver functions in resected rats.
Kaminsky (1975) used Wistar rats to study the effect of 79% small intestinal bypass on hepatic lipogenesis, while comparing a normal diet (<5% fat) and a high-fat diet (18% fat). In 1979 he reported an investigation of hepatic lipid metabolism following distal ileal bypass (50%) in both exogenous hypercholesterolemic rabbits and Zucker rats.
Nelson (1976) compared liver morphology and intestinal microflora in conventional and germfree dogs after jejunoileal bypass.
Tilson (1969,1972,1976,1980), Fenyö(1976), Simmons(1975) Sachdev (1979) Mc.Gouran (1978, 1979), Rutter (1978) and Tuma (1978) used Wistar (Sprague-Dawley) rats whereas Sclafani

(1978) used VMH rats, which were made obese by a ventromedial-hypothalamic lesion,and a small group of Zucker rats. Branch (1980) compared dogs with a Payne shunt and dogs with a jejunoileal bypass, the distal end of the bypassed segment being exteriorized as an ileal stoma.
Pector et al.(1981) studied the effects of portacaval shunt in the genetically obese Zucker rat.

2.2 Choice of experimental model

From all animal models mentioned above the Zucker rat or "Fat rat" appeared to be the most appropriate (Zucker, 1961).
Since jejunoileal bypass is developed as an ultimate treatment of morbid obesity in man, the animal should also be obese, if possible through overeating.It should also be accessible for surgery, and available in sufficient numbers, both male and female, for statistical analysis without being too expensive in its procuring and support.
The Zucker rat fulfils all these demands but is rather fragile considering the 20% anastomotic leak rate and the 30% mortality rate, reported by Grosfeld (1976).
However, anastomotic leaks being partly considered a technical failure the use of an operating microscope may improve the results.

2.3 The genetically obese Zucker rat

Extensive reviews of the literature about the genetically obese Zucker rat, were given by Bray (1977) and de Waard (1978).

2.3.1 Genetics

In 1961, Zucker (L.M.) and Zucker (T.F.) discovered a spontaneous mutation in the 13 M rat strain of the brown rat (Rattus norvegicus), which was a crossbred from the Sherman and Merck strains . The obesity is inherited as an autosomal recessive mendelian trait: approximately 25% of the progeny of carriers of the gene for fatness (fa), either male or female, become obese after three weeks of age.
The obese rats (fa/fa) differ from their lean littermates (Fa/fa; Fa/Fa) in that most males and most females are sterile.

2.3.2 Food consumption and food efficiency

The fatty rats develop an increased food consumption of 40%-50%, compared with their lean littermates (Zucker, 1962; Barry,1969; Bray, 1972; Becker, 1977; Grosfeld, 1977; Pector, 1981). Also food efficiency in obese rats is higher than in lean littermates (Zucker, 1967).

2.3.3 Growth and body weight

Zucker(1961) and Powley (1976) give mean weight curves for fatty male and female rats and their lean littermates over a period up to 40 weeks and 18 weeks respectively. These curves differ only slightly.
In obese rats of three to four months old, the fat percentage

approximates 50%. It does not increase further, although the rats still gain weight during the first year of their lives (Zucker, 1963).
Body weight may rise to over 1000 grams. The difference in body weight between obese and lean rats is mainly caused by a different mass of fat (Zucker,1967; Johnson , 1971; Bray, 1973). The increase in mass of fat is not only the result of an increased food intake, but is also due to increased food efficiency. Increased food efficiency means a lower heat production and an enhanced lipogenesis in early life as a result of an inborn error in protein metabolism with a tendency to a lower deposition of body protein (Pullar, 1974; Bray ,1974).

2.3.4 Blood lipids

The lipid content in the blood of the obese Zucker rat is increased (Zucker, 1961,1962,1965,1972; Bach, 1977), in particular with regard to the triglyceride concentration. Even after an overnight fast the rats were found to have triglyceride concentrations of 1000 mg per 100 ml blood or even more (Zucker,1962; Barry,1969). Whereas lean littermates have cholesterol concentrations of 80-90 mg per 100 ml blood, obese Zucker rats have cholesterol levels up to about 250 mg per 100 ml blood.
The levels of very-low-density lipoproteins (VLDL) are seven times as high and those of low-density lipoproteins (LDL) and high-density lipoproteins (HDL) are twice as high as in the serum of lean littermates (Schonfeld,1974).
Zucker rats have a primary excessive liver protein synthesis and hypertrophy of the liver. In early life excessive serum proteins are found and a slowly developing tendency, at a later stage, to proteinuria and hypoalbuminemia due to progressive glomerulonephrosis, was demonstrated by Zucker (1965).

2.3.5 Endocrine aspects

A further discussion of endocrine aspects of the Zucker rat is beyond the scope of this thesis. A good compilation is given by Bray (1977) and de Waard (1978).
Zucker rats are hyperinsulinemic but normoglycemic, show reduced levels of glucagon, hypothyroidism and an impaired reproductive function. Only Martin (1978) finds serum glucose elevated.

2.3.6 Summary

The Zucker (fatty) rat inherits obesity as an autosomal mendelian recessive trait. The rat is obese, hyperphagic, hyperinsulinemic but normoglycemic. The significant hypertriglyceridemia is due to the increased hepatic production of very-low-density lipoproteins. Hypercholesterolemia is moderate. The reproductive function is impaired.

EXPERIMENTAL DESIGN

3.1 Pilot study

To become conversant with expected and unexpected problems and to gain experience with the operating microscope, a pilot study was performed on 25 Wistar rats in January 1978.
Several forms of anesthesia were used : ether inhalation, Vetalar i.m. + Rompun s.c. + atropine i.m. , Nembutal intraperitoneally, and Hypnorm + Valium i.m.. Nembutal proved to be most suitable.
Preoperative weight (309 ± 90g, mean ± s.d.)and body length (21.5 ± 2.0 cm , mean ± s.d. , nose to anus) were recorded in anesthesia.
After midline celiotomy measurement of the small bowel from the ligament of Treitz to the cecum (71.3 ± 11.5 cm , mean and s.d.) was performed twice, at the mesenteric side, stretching the mesenterium as much as possible without tearing.
Nylon 3-0, a supple piece of solder wire (ø2mm) and Supramid 1, a plastic fibre, were used.
Supramid 1 proved to be best being sufficiently supple and not stretchable.
An end-to-end anastomosis between the proximal 5 cm of jejunum and distal 8 cm of ileum was accomplished with interrupted 8-0 Ethilon sutures with the help of a microscope. The proximal end of the excluded small bowel was oversewn and the distal end was anastomosed end-to-side to either the ascending or the transverse or the descending colon with interrupted 8-0 Ethilon sutures.
Specimens for histologic examination were taken from jejunum, ileum and liver. Wedge biopsies were taken from the liver, being easier to obtain and yielding more liver tissue than those obtained by needle aspiration.
Stretching the wet intestinal sample on dry drawing-paper made it sufficiently adhesive after a few minutes in the air, and afterwards in 4% formaldehyde, for histologic examination. This procedure is less time-and-space-consuming than pinning the sample on cork or wax.
Five rats died during operation or the following night on account of anesthetic problems.
One rat died after five weeks showing acute pancreatitis.
One rat died after seven weeks because of a volvulus of the cecum. The animal had partly been eaten by other rats.
Three rats had to be killed because of too great a loss of weight and cachexia.
Fifteen rats were sacrified between two and four months postoperatively. These animals showed a rapid decrease of weight until 4 ± 1.2 weeks (mean ± s.d.), followed by slow increase of weight, a steady state or a very slow decrease of weight and consequently slow increase of weight.

At time of death, all rats had macroscopically clear hypertrophy of the functional part of the small intestine, clear hypotrophy of the bypassed small intestine, enormous distension of the cecum and normal livers.
In this pilot study Nembutal,administered intraperitoneally, proved suitable as anesthesia for rats when one is using an operating microscope.
Experience was gained in measuring the small intestinal length with Supramid 1, in using an operating microscope to construct intestinal anastomoses and in suturing the liver, after the cutting out of a wedge.
Weight plots showed a dip after 4 $\pm$ 1.2 weeks (mean $\pm$ s.d.) and mostly a slow increase of body weight afterwards. Sixteen weeks would be sufficient to evaluate the effect of this operation on weight.
All rats had to be individually housed because of the possibility of cannibalism.
The rats showed hypothermia immediately after operation.Since this might be a factor causing postoperative deaths, a heating mattress was used.
Apart from these answers some questions arose. What layer of the small intestine would be responsible for hypertrophy and hypotrophy. Why such a distension of the cecum and what layer would be involved?

3.2 Study of Zucker rats

3.2.1 Grouping according to the type of operation

Four types of operation were performed (see 3.3):

- Group I : Sham operation, including biopsies of jejunum, ileum and liver, followed by end-to-end anastomoses of jejunum and ileum, and by suturing of the liver.
- Group II : A standard jejunoileal end-to-end shunt, leaving 4 centimetres of jejunum and 2 centimetres of ileum; the same biopsies as in group I are taken.
- Group III : A 10% jejunoileal end-to-end shunt, leaving two thirds of this 10% of jejunum and one third of this 10% of ileum.
  Thus 90% of the small intestine is excluded. In the literature this bypass is called a 90% jejunoileal bypass since 90% of the small intestine has been bypassed. We will stick to the term 10% bypass analogous to the 4+2 cm jejunoileal bypass and the 14-4 inch bypass as used by Payne and Scott.
  The same biopsies as in group I are taken.
- Group IV : An end-to-side portacaval shunt,including the same biopsies as in group I.

3.2.2 Age and sex of animals

Since morbid obesity occurs in both men and women we used male and female Zucker rats to study the effects of the operative procedures on both sexes.
Grosfeld (1976) only used male Zucker rats in his jejunoileal

bypass experiment, whereas Madura (1975) and Grosfeld (1977) did not mention the sex of their Zucker rats.
Since it was impossible to breed sufficient Zucker rats of the same age and weight at operation, knowing that, on average, one out of four young rats would become obese, the types of operation were equally distributed over the rats, male as well as female. Operations were performed in the period of September - December 1978. Only for the portacaval shunt group, as operated upon at the end of the experimental period (December 1978), the age differed from that of the other three groups (see chapter 4.6.2).

3.2.3 Housing

The Zucker rats were bred within the "Centre for small laboratory animals " of the Agricultural University of Wageningen, The Netherlands.
During the experimental period they were housed in the "Central Animal Laboratory " of the University of Nijmegen, The Netherlands.
Until the day of operation the Zucker rats were housed in metal cages with wired floors ,males and females separately.
After operation the rats were maintained individually in hard plastic cages (38 x 26 x 16 cm, RUCO, Waalre, The Netherlands) with wood-wool for bedding.
Rats in the study sub 3.2.11 were kept in metabolic cages where day and night periodicity was changed.
A standard rat chow, RMH-B, (Hope Farms Company, Woerden, The Netherlands) containing approximately 22% protein, 6.5% fat, 4.2% crude fibre and traces of cholesterol, and water were fed ad libitum. Room temperature was kept at 22 degrees Centigrade and relative humidity at 65%. The room was ventilated. The illumination of the room was artificial, with a day and night periodicity changing at 07.00 a.m. and at 19.00 p.m. every 24 hours.

3.2.4 Blood sampling

A few weeks before operation, approximately 7 weeks after operation and 16 weeks after operation blood samples were taken by orbit puncture with the help of a capillary glass tube. The rats were fasted overnight and were kept under light ether anesthesia during the procedure.
Hemoglobin (Hb), serum bilirubin, serum glutamic pyruvic transaminase (G.P.T. or A.L.A.T. = Alanine Amino transferase), serum alkaline phosphatase, serum cholesterol and serum triglycerides were measured.

3.2.5 Weighing

The rats were weighed immediately before operation, postoperatively every day for two weeks and then once a week, until sacrifice at sixteen weeks.

3.2.6 Anesthesia

We studied the effects of ether, Vetalar i.m. + Rompun s.c. + atropine i.m. , Hypnorm and Valium i.m. and Nembutal,intraperitoneally ,in Zucker rats.
All anestetics had to be administered in a high dose to be

effective and the rats showed a long postoperative period of recovery and in some cases died. Nembutal, administered intraperitoneally, proved suitable. After adding Megimide, an analeptic, postoperatively, the rats quickly awoke and mortality dropped considerably. Micoren was not as effective as Megimide and therefore not used anymore.

3.2.7 Measurement of body length

In anesthesia the body length of the rats was measured from nose to anus. As a standard procedure the legs of the rat, in supine position, were fixed with adhesive tape to a heating mattress.
After 16 weeks the same procedure was taken.

3.2.8 Measurement of intestinal length

The length of the duodenum (pylorus to ligament of Treitz) and the small intestine (ligament of Treitz to cecum) was measured in all rats, with Supramid 1. Measurement was executed twice at the mesenteric side, stretching the mesenterium as much as possible without tearing.
The cecum was measured at the mesenteric and at the antimesenteric side.
After 16 weeks the lengths of the duodenum, the functional shunt and the cecum were measured in anesthesia.

3.2.9 Histologic examination

Biopsies were taken of liver, jejunum and ileum during operation.
After 16 weeks the same procedure was taken in anesthesia for the sham rats and portacaval shunt rats whereas in the 4 + 2 cm shunt rats and 10% shunt rats biopsies were taken of the functional shunt, the bypassed jejunum and the bypassed ileum. The cecum of all rats could only be examined after 16 weeks.
The wet intestinal specimens were stretched on dry drawing-paper, dried for a few moments in the air and fixed in 4% formaldehyde. After ample fixation in formaldehyde one end of the specimen was cross-sectioned , embedded carefully in paraffin and sectioned at 4 Mu on a plane transversely to the lumen,resulting in a circular preparation.
Those samples which did contain an anastomosis had both ends cut off on a plane transversely to the lumen, as far away from the anastomosis as possible. The same circular preparations as mentioned above were the result. The remaining and larger part of the specimen was sectioned longitudinally to the lumen into two halves and one half carefully embedded in paraffin and sectioned at 4 Mu on a plane longitudinally to the lumen. This way all anastomoses could be examined.
All preparations were stained with haematoxylin and eosin. Liver biopsies were fixed in 4% formaldehyde, embedded in paraffin, sectioned at 4 Mu and stained with Azan, Periodic acid-Schiff and Perls.

3.2.10 Cecomegaly

Apart from measuring the circumference of the cecum some anaerobic bacterial cultures were performed.

3.2.11 Gastro-intestinal transit time

In some rats the gastro-intestinal transit time was studied by means of the quantitative recovery of a dye (carminic acid) and of minute steel balls in the feces after intragastrical application.

3.2.12 Analysis of mortality

As liver failure is a serious complication of jejunoileal bypass mortality was given careful study.

3.2.13 Various changes after jejunoileal bypass

To study early changes in liver and intestine after bypass some rats were killed after one week and after two weeks.
After 16 weeks other remarkable changes were recorded like macroscopical hypertrophy of the functional shunt, hypotrophy of the bypassed segment, condition of hair, occurrence of perianal ulceration and occurrence of incisional hernia. Results will be given throughout the various chapters.

3.3 Operative procedures

3.3.1 Common part of procedures

After overnight fast the Zucker rat was weighed. Nembutal (Pentobarbital, Abbott), 6 mg/100 g was administered intraperitoneally and after two to six minutes the rat was anesthetised.
The abdomen was shaven and the legs of the rat, in supine position, were fixed with adhesive tape to a heating mattress. Body length from nose to anus was measured with a plastic ruler and recorded together with date of birth, sex, weight, date of operation, time of beginning and end of operation, amount of anesthesia, preoperative blood parameters, type of operation and measurements of intestine, as will be described below.
Celiotomy was performed with clean instruments, sterilised once a day. Since each day four rats were operated , this was essentially a non-sterile technique.
Supramid 1 (Supramid 1, sterilised, 75m. Art.-No 118 407 , B.Braun Melsungen A.G., Made in W.Germany) was placed along the mesenteric border of the duodenum from pylorus to ligament of Treitz and the length was recorded. From the ligament of Treitz the small intestine was measured along the mesenteric border, stretching the intestine as much as possible without tearing the mesenterium or damaging the intestine, in consecutive steps to the cecum. This measurement was repeated and the mean value recorded as small intestinal length.
The length of the cecum was measured along the mesenteric and antimesenteric border without any stretching and both values were recorded.
At this point it was decided which of the 3 types of operation would follow : sham operation, 4+2 cm shunt or 10% shunt.
This would depend on the number of surviving rats of previous operations.

3.3.2 Sham operation

Approximately 5 cm distal of the ligament of Treitz about 2 cm of jejunum were excised and an end-to-end anastomosis was constructed with a single, inverting layer of interrupted No. 8-0 monofilament Ethilon sutures, while using an operating microscope (Stereoscopic operating microscope, Zeiss OPMI I, Germany, magnification ranging from x 6 to x 40 with standard lenses).
This procedure was repeated for an ileum biopsy about 5 cm proximal of the cecum (see fig. 6.3).
A wedge of liver of about 1 cm x 0.5 cm was cut out of the most prominent liver lobe with a pair of scissors and this wound was repaired with two 8-0 Ethilon sutures.

3.3.3 Operation of 4 + 2 cm shunt

The jejunum , was divided 4 cm distal of the ligament of Treitz, as measured along its mesenteric side. Approximately 2 cm of jejunum was taken as biopsy of the proximal excluded part and this proximal excluded small bowel was closed with a 8-0 Ethilon purse-string suture.
The ileum was divided 2 cm proximal of the cecum, measured along its mesenteric side. Approximately 2 cm of ileum of the distal excluded part was removed as a biopsy specimen.
An end-to-end anastomosis was constructed between the proximal 4 cm of jejunum and the distal 2 cm of ileum with a single, inverting layer of interrupted No 8-0 monofilament Ethilon sutures, while using an operating microscope (see fig. 6.4).
The distal excluded end of ileum was anastomosed end-to-side to the ascending colon with a single, inverting layer of No 8-0 monofilament Ethilon sutures.
Liver biopsy was taken as in the sham operation.
Jejunal and ileal part as well as the total length of the bypass were measured before the closing of the abdomen.

3.3.4 Operation of 10% shunt

Two-thirds of 10% of the small intestinal length were measured along the mesenteric border of the proximal jejunum, starting from the ligament of Treitz, and the jejunum was divided.
One third of 10% of the small intestinal length was measured along the mesenteric border of the distal ileum, starting from the cecum, and the ileum was divided.
In the same way as in the 4 + 2 cm shunt the anastomoses were constructed after taking biopsies of jejunum, ileum and liver and the measured length of the bypass was recorded (see fig. 6.4).

3.3.5 Operation of portacaval shunt

After measuring and before taking biopsies as described for the sham operation, overlying retroperitoneal fat tissue was dissected from the inferior caval vein for proper exposure at the level of and proximal of the right renal vein. An operating microscope was used.
The portal vein and its nearest branch, the right gastric vein, were ligated and transsected as closely as possible to the liver. To prevent engorgement of the small intestine the mesenteric artery was temporarily occluded by a vessel clip.

The inferior caval vein was partly occluded by a vessel clamp and the portal vein was completely occluded by a vessel clamp. After excising a small ellipse out of the inferior caval vein an end-to-side anastomosis was performed between portal vein and inferior caval vein with a running, everting No 8-0 monofilament Ethilon suture.
After the removal of all vessel clamps and after the obtaining of the required biopsies the abdominal wall was closed.

3.3.6 Common closing procedure

Closing procedure was standard for all operations.
The abdominal wall was sutured with Tevdek 2-0 (Tevdek, Deknatel, New York, U.S.A.) with the help of a lock-stitch for peritoneum and rectus muscles and a horizontal mattress suture for the skin.
Ten millilitres of warm normal saline (0,9% NaCl) and Megimide, 2 mg/100 g ("Megimide" = Bemegride B-ethyl-B-methylglutarimide in normal saline 5 mg/ml, Nicholas Laboratories Ltd. , Bath Road, Slough, Bucks, England) were injected intra peritoneally.
Overnight the rats were placed under a heating lamp because, even with a heating mattress, the rectal temperature was only 33 degrees Centigrade postoperatively.

PRE- AND POSTOPERATIVE VALUES OF RELEVANT PARAMETERS AND CHANGES OF WEIGHT INDUCED BY THE VARIOUS OPERATIONS

4.1 Introduction

In this chapter the 4 groups of Zucker rats, each undergoing a different operation, will be compared with respect to sex, age, body length, length of small intestine, length of shunt (if constructed) and weight. Postoperative values will be given and a multiple regression model will be presented, incorporating the preoperative age, small intestinal length, weight, sex and the shunt percentage. This model should predict the loss of body weight 16 weeks after jejunoileal bypass.
All statistical calculations have been performed under responsibility of the Department of Statistical Consultation (M.S.A.) of the University of Nijmegen.

4.2 Number and sex of Zucker rats in the various experimental groups

The total number of Zucker rats was 145, 139 fatty male and female rats, and 6 male lean littermates. The 139 fatty rats are to be divided into

63 rats, killed 16 weeks postoperatively, constituting the experimental groups;
10 rats, which were kept in a metabolic cage for some time to measure gastro-intestinal transit time;
12 rats, 5 of which were killed 1 week and 7 of which were killed 2 weeks after construction of a jejunoileal bypass to study its early effects ;
54 rats, deceased or killed during operation or within 16 weeks after operation.

Thus, 63 rats were classified for being used in the experimental groups:
Group I : sham operation, 10 rats, 4 male and 6 female
Group II : 4 + 2 cm shunt, 20 rats, 10 male and 10 female
Group III: 10% shunt, 23 rats, 10 male and 13 female
Group IV : portacaval shunt, 10 rats, 5 male and 5 female.
It appears that both sexes are nearly equally present in the four operation groups.

4.3 Age

4.3.1 Age at operation

Table 4.1 shows the mean age of the 63 fatty rats on day of operation, both for each experimental group and for all rats taken together.

type of operation	*N*	*age*	*s.d.*
sham	*10*	*114*	*± 26*
4 + 2 cm	*20*	*118*	*± 22*
10%	*23*	*121*	*± 15*
p.c.s	*10*	*140*	*± 2*
all operations	*63*	*122*	*± 20*

Table 4.1 Mean age and s.d. at operation (in days) of the experimental groups.

The mean ages for the sham-, 4+2 cm- and 10% group are nearly equal, but the mean age for the p.c. shunt group is clearly higher.
This difference is caused by the fact that the p.c.shunt operation was performed at the end of the operation period, while the sham-, 4+2 cm- and 10% operations were performed alternately.

The mean age of all rats taken together was 122 days. Looking at the weight plot of Zucker rats as given by Zucker in 1961, we notice that this age means that the rats are adult and that the fat percentage of approximately 50% does not increase further, although the rats still gain weight (see 2.3.3).

4.3.2 Time between operation and sacrifice

It was a practical impossibility to sacrifice each rat exactly 112 days after the operation.
Therefore, the time between operation and sacrifice varies between 109 and 119 days.

4.4 Body length

4.4.1 Body length at operation

Table 4.2 shows the mean body length for the 63 fatty rats in the four operation groups.

type of operation	N	body length	s.d.
sham	10	198	± 12
4 + 2 cm	20	202	± 12
10%	23	201	± 12
p.c.s	10	212	± 8
All operations	63	203	± 11

Table 4.2 Mean body length and s.d. at operation (in mm) of the experimental groups.

Male rats appear to be significantly longer than female rats ($p < 0.001$, Student's two sample test, results not shown). The rats in the p.c.s. group were longer than the rats in all other groups. This difference is probably caused by their somewhat more advanced age (4.3.1).

<u>4.4.2 Change of body length after 16 weeks</u>
The body length of the rats was measured again, 16 weeks postoperatively. The average change per group is given in table 4.3. Changes were essentially the same in male and female rats (see below). Therefore, groups have been compared as a whole.

	sham N = 10	4+2 cm N = 20	10% N = 23	p.c.s N = 10
change body length	+20 ± 6	-4 ± 9	+5 ± 6	+7 ± 5
p-value	< 0.001	0.04	< 0.001	0.002

Table 4.3 Change of body length after 16 weeks (mean and s.d. in mm , p-value according to Student's paired test).

In all groups there was a significant difference between length at operation and length 16 weeks later.
Clearly, the sham rats have been gaining length considerably, while the 10% and the p.c.s. rats only gained length slightly. The 4+2 cm rats even diminished in size generally.
Classifying the rats according to sex and operation we also applied a two-way analysis of variance. No significant differences regarding sex were found. However, the hypothesis that averaged over both sexes the 4 operations give rise to the same change of length, has to be rejected ($p < 0.001$). A simultaneous multiple comparison method according to Scheffè reveals that this has mainly been caused by the fact that each

group differs significantly from one of the others ($p \leq 0.002$) excepting the 10% shunt group compared to the p.c.s. group.

4.4.3 Discussion

Grosfeld et al. (1976) constructed in 10 male, 8 week-old, (125 g) Zucker rats an end-to-end jejunoileal bypass between 8 cm of jejunum and 5 cm of ileum, leaving 10% of the small intestine functional. Four months later calliper measurements of the thoracolumbar vertebral column were performed.
Skeletal development was retarded significantly in bypassed rats as compared with controls: vertebral column of 125.9 ± 3.5 mm and 138.3 ± 3.9 mm, respectively ($p < 0.025$), a difference of 12.4 mm.
This figure of 12.4 mm growth retardation fits reasonably well with our results for,older, Zucker rats (table 4.3). We find a mean difference of 15 mm between sham group and 10% group.

4.4.4 Conclusion

A 4+2 cm jejunoileal bypass has a significant shortening effect on body length in an adult, but still growing, rat if compared to a sham operated rat.
Both the 10% jejunoileal bypass and the p.c.shunt have the same effect though to a lesser degree.

4.5 Length of small intestine and duodenum

4.5.1 Length of small intestine of fatty rats at operation

The construction of the 10% shunt was dependent on the small intestinal length (see 3.3.4). Therefore, the length of the small intestine was measured twice at the mesenteric part of the intestine (see 3.1, 3.2.8 and 3.3.1). The mean value was taken to represent the actual intestinal length (table 4.4 and 4.5). Measurements were performed immediately after celiotomy.

first measurement	:	*913 ± 113*
second measurement	:	*905 ± 115*
1st and 2nd measurement	:	*909 ± 113*

Table 4.4 Mean length and s.d. of small intestine at operation (in mm) in 139, male and female, fatty Zucker rats.

male rats (69)	:	*961 ± 99*
female rats (70)	:	*857 ± 103*

Table 4.5 Mean length and s.d. of small intestine at operation expressed in mm in 139 male and female fatty Zucker rats.

On the average small intestines in males were significantly longer than those in females (Student's two sample test, $p \leq 0.001$).

4.5.2 Length of small intestine of lean littermates

Also the small intestinal length of 4 male lean littermates with a mean age of 131 days (s.d. = 3 days) was measured twice.
The average length was 898 mm (s.d. = 44 mm), each separate value again being derived from two consecutive measurements.
This means that the small intestine in male fatty rats (table 4.5) is significantly ($p < 0.001$, Student's two sample test) longer than the small intestine in their male lean littermates with a mean body length of 222 mm (s.d. = 5 mm).

4.5.3 Length of duodenum

The average length of the duodenum at operation was 61 mm for the 63 male and female fatty Zucker rats of the experimental groups.
The average length of the duodenum 16 weeks postoperatively was 66 mm for these rats.
This increase of length of duodenum after 16 weeks is not significantly different for the 4 operation groups according to a two-way analysis of variance, when the rats have been classified on a basis of sex and operation.

4.5.4 Discussion

The construction of a jejunoileal bypass is based on the theory that shortening of the functioning small intestine will cause loss of weight.
A certain length of functioning jejunum and ileum will provide the desired loss of weight without too much morbidity and without mortality. When a jejunoileal bypass is too short intractable diarrhea will follow as in a short bowel syndrome.
The method of measurement therefore is very important in constructing a jejunoileal bypass because a few centimetres more or less makes all the difference between insufficient loss of weight and too much loss of weight and even death. A loss of weight of 30% of preoperative weight is generally considered as satisfactory.
For instance, Juhl et al.(1974) constructed an end-to-side jejunoileal bypass using either 37 or 34 cm of jejunum and 13 cm of ileum. The reduction of functioning small intestine from 50 to 47 cm increased loss of weight by 25 kg in one and a half year.
Ravitch et al.(1979) reported that 3 years after an end-to-end jejunoileal bypass the loss of weight of 52 patients with 45 cm or less functioning intestine was at least one third of the preoperative weight whereas out of 12 patients with 47.5 cm or more functioning intestine only 3 lost that much.
Another reason why it is important to know the method of measurement is that it allows the possibility of comparing results of the various authors. Regrettably,the method of measurement is not always described .
So far only a few authors have reported a correlation between loss of weight and intestinal length (Guzman et al., 1975,

Backman, 1975, Benfield et al., 1976). Salmon (1971) could find no direct relation between either length of intestine and original weight or between percentage of intestine excluded and loss of weight in 10 dogs.
Backman and Hallberg (1974) measured small intestinal length in 88 subjects during abdominal operations. They used a moistened cotton band which they placed on the surface of the intestine between the mesenteric and antimesenteric border. Measurements were always performed twice, and sometimes three times. The second measurements always gave lower values, on the average 9.3% (s.d. = 0.7%) of small intestinal length. The third measurement gave values similar to those obtained by the second measurement.
We have experienced the same phenomenon in our fatty rats, although to a far smaller degree. On the average the second measurement resulted in a value which was 8 mm , or 1% , lower than the result of the first measurement (separate results are not shown).
Backman's explanation for the second measurement being lower seems reasonable. By handling the intestine during the first measurement contractility in the intestinal wall increases. Stretching of the intestinal wall directly induces contractility in the smooth muscle and thus effects the release of serotonin in the intestinal wall. Serotonin is known to increase the reactivity, which can result in contractions in smooth muscle cells (Bockus, 1964).
Backman also found small intestinal length to be significantly greater in morbidly obese patients: mean length for obese men was 8.24 metres and in the control group 6.98 metres; corresponding values for women were 7.34 and 6.16 metres, respectively.
The same holds good for obese and lean Zucker rats : 961 $\pm$ 99 mm versus 898 $\pm$ 44 mm , a difference of 63 mm .
Backman gives interesting but speculative explanations for the correlation between overweight and a long small intestine: either a primary congenital long intestine or a secondary reaction to an adaptive mechanism like overfeeding or endocrine compensation.

4.5.5 Conclusion

The mean length of the small intestine of male fatty rats, calculated as the average of two consecutive measurements along the mesenteric border, is significantly greater than that of female fatty rats. Also, male fatty rats have a significantly longer small intestine than their lean littermates.

4.6 Length of the constructed 4+2 cm and 10% jejunoileal bypass and changes in length of the bypass after 16 weeks

4.6.1 Introduction

Madura et al.(1975) and Grosfeld et al.(1976 and 1977) describe a 90% jejunoileal bypass in adolescent male fatty Zucker rats, weighing 125 grams and in fatty Zucker rats, weighing 500 - 600 grams.
A 90% jejunoileal bypass was accomplished with an end-to-end anastomosis between the proximal 8 cm of jejunum and the

distal 5 cm of ileum. Small intestinal length was not mentioned neither was the exact way of measuring described, so one should conclude that for male rats of 125 g and rats of 500 - 600 g small intestinal length is the same being 130 cm. Younoszai (1978) shows that in young male albino rats of 50 to 80 g body weight and small intestinal length are different after a 5-week period if they are fed different diets.With a normal diet body weight is 273 g and the length of the small intestine is 115 cm. This measurement was performed post mortem, after flushing the intestine and stripping it from the mesentery. It means that in the living rat the length of the small intestine would be shorter.
Miller (1971) demonstrates a positive significant correlation between small intestinal length and body weight in Sprague-Dawley male albino rats. Measurements were done after the mesentery had been stripped. During adolescence the small intestine grows rapidly until it reaches 75% of its adult length (80 cm),and arrives at a maximum percentage of nearly 5% (3.0 g) of the body weight (60 g) at the age of 20 days.
At 125 g (age 30 to 35 days) it is almost fully developed:
a length of 95 cm , a weight of 5 g and 4 % of the body weight.
From this stage it only lengthens 10-20 cm and increases in weight by 1-2 g. Considerable divergence, however, was revealed among individual animals, e.g. a rat weighing 300 g may have a small intestinal length ranging from 90 to 130 cm.
Baggio (1976), Armellini (1976) and Ottolenghi (1976) performed a jejunoileal bypass in Sprague-Dawley rats fattened with insulin. The mean small intestinal length was 145 cm . By constructing an end-to-end anastomosis between the proximal 4 cm of jejunum and the distal 2 cm of ileum approximately 95% (in fact 96%) of the small intestine was excluded. The exact way of measuring was not described.
Based on these experiments two end-to-end jejunoileal bypasses with different lengths of functional small intestine were accomplished : a 4+2 cm shunt and a 10% shunt.
After construction of the bypass the length of the functional part was measured at the mesenteric border of the intestine.

4.6.2 Length of the bypass at operation

Table 4.6 gives the length of the bypass for jejunal and ileal part, taken separately and together.

	4+2 cm (N = 20)	10% shunt (N = 23)
jejunum	42 ± 2 4.7%	58 ± 7 6.5%
ileum	21 ± 3 2.3%	30 ± 5 3.3%
jejunum + ileum	64 ± 5 7.0% ± 0.7%	88 ± 10 9.8% ± 0.5%

Table 4.6 Mean length of functional intestine in mm (± s.d.). The mean lengths of jejunum and ileum have also been expressed in percentage of the mean total small-intestinal length, while for the total bypass the mean percentage (± s.d.) has been given.

It shows that a 4 + 2 cm jejunoileal bypass actually means a 7% jejunoileal bypass, so 93% of the small intestine is not functioning any more.

4.6.3 Change in length of the bypass after 16 weeks

According to a two-way analysis of variance, where the rats were classified on a basis of sex and type of operation, no significant influence of sex was found, neither with respect to the change of length of the jejunal part nor with respect to the change of length of the ileal part of the bypass.
Therefore, the groups are presented as a whole, neglecting sex difference, in table 4.7 .

	4 + 2 cm (N = 20)	10% shunt (N = 23)
Δ jejunum	6 ± 9	9 ± 14
	14%	16%
Δ ileum	4 ± 5	6 ± 8
	20%	21%
Δ jejunum + ileum	10 ± 11	16 ± 19
	16%	18%

Table 4.7 Change in length (Δ) of functional segment for jejunal and ileal part of the bypass and of the total functional bypass, 16 weeks after operation in mm (± s.d.) and expressed as percentage of the mean length of the part of the bypass at operation.

Clearly, the length of the functional intestine increases after both types of operation. All changes are significant ($p \leq 0.01$, Student's paired test).
The relative increase appears to be more pronounced in the ileal part of the functional bypass. Possibly, this segment adapts more strongly because it has to compensate for a greater loss of absorbing surface area.

4.6.4 Change in length of the bypass in the 4+2 cm jejunoileal bypass group, 1 , 2 and 16 weeks postoperatively

Among the rats with a 4 + 2 cm jejunoileal bypass, five were sacrificed after 1 week and six after 2 weeks. The change of length of the functional ileal and jejunal segments, and thus the change of length of the total functional small intestine, was compared with the data obtained from the rats killed after 16 weeks (table 4.8).
Using a one-way analysis of variance we find that the

hypothesis of equal changes of the total bypass for the 3 groups with a 4+2 cm jejunoileal bypass has to be rejected ($p = 0.006$). According to a multiple comparison method of Scheffé this is mainly caused by a significant difference between the 2-week group and the 16-week group ($p = 0.01$). Similar results are found with respect to the ileal part and jejunal part separately.

	1 week (N = 5)	*2 weeks (N = 6)*	*16 weeks (N = 20)*
Δ jejunum	*1 ± 6*	*-4 ± 5*	*6 ± 9*
	2%	*10%*	*14%*
Δ ileum	*-1 ± 5*	*-1 ± 4*	*4 ± 5*
	4%	*7%*	*20%*
Δ total segment	*0 ± 10*	*-6 ± 6*	*10 ± 11*
	0%	*9%*	*16%*

Table 4.8 Change (Δ) in length of bypass for jejunum, ileum and jejunum+ileum in rats killed 1, 2 and 16 weeks after 4+2 cm jejunoileal bypass. Values are given in mm (± s.d.) and as percentage of the mean value immediately after completion of the bypass.

Apparently, neither the total length of the bypass nor the separate segments of the bypass have changed clearly after 1 week. After 2 weeks the total length of the bypass has decreased by 9% which is remarkable since after 16 weeks it has increased by 16%. In other words, after 2 weeks the total length of the bypass is 91% of the operative value and after 16 weeks 116%. Thus, between 2 weeks and 16 weeks postoperatively, the functional part of the small intestine increases by almost 30%. This illustrates the great adaptive capacity of the small intestine.

4.6.5 Summary

The average length of the 4+2 cm jejunoileal bypass in the fat Zucker rat was 7.0 ± 0.7% of small intestinal length, the average length of the 10% jejunoileal bypass was 9.8 ± 0.5%.
The functional part of the small intestine, both in the 4+2 cm group and in the 10% group, was significantly enhanced 16 weeks postoperatively (16% and 18% respectively).
The relative increase was possibly slightly greater in the ileal part than in the jejunal part of the bypass.
Examination of the 4+2 cm group indicates that this process only occurs from two weeks after operation.

4.7 Body weight

4.7.1 Body weight of fatty and lean Zucker rats at operation

The mean preoperative weight of the fatty Zucker rats in the experimental group (N = 63) was 354 grams, (s.d. = 61 grams). The mean preoperative weight of the male fatty Zucker rats (N = 29) in this group was 384 grams (s.d. = 49 grams) and the mean preoperative weight of the female fatty Zucker rats was 328 grams (s.d. = 59 grams).
The mean preoperative weight of the male lean Zucker rats (N = 6) was 292 grams (s.d. = 21 grams) at a mean age of 127 days (s.d. = 7 days).

4.7.2 Relative body weight changes following operation

For two weeks after operation, weight of the rats was recorded daily and thereafter once a week until sacrifice after 16 weeks.
In order to compare the effects of the various operations results are expressed as the percentage change from preoperative weight. Figure 4.1 depicts the average weight changes after the four types of operation.
The sham rats gain weight in an almost linear way. The rats with a 4+2 cm shunt lose weight gradually over a period of 9 weeks. Thereafter their weight remains stable. Rats with a 10% shunt have lost about 9% of their preoperative weight after three weeks and then start to grow again.
The weight of the rats with a portacaval shunt hardly changes during the period of investigation.

4.7.3 Body weight changes after 16 weeks

The average change of body weight 16 weeks postoperatively compared to preoperative weight in the various groups is presented in table 4.9 .

	N	*Δ weight (%)*	*Δ weight (g)*	*p-value*
sham	*10*	*66 ± 30*	*194 ± 40*	*< 0.001*
4+2 cm	*20*	*-23 ± 19*	*- 84 ± 69*	*< 0.001*
10%	*23*	*6 ± 14*	*25 ± 35*	*0.003*
p.c.s.	*10*	*6 ± 10*	*28 ± 41*	*0.06*

Table 4.9 Mean weight changes (Δ) 16 weeks postoperatively in the four groups (values in grams and percentage of preoperative weight ± s.d.). P-values as results of Student's paired test for an examination of the difference between pre- and postoperative weight are given.

Weight change at the end of the 16-week postoperative period was quite significant in each group, with exception of the p.c.shunt group. However, the actual effect of the allegedly

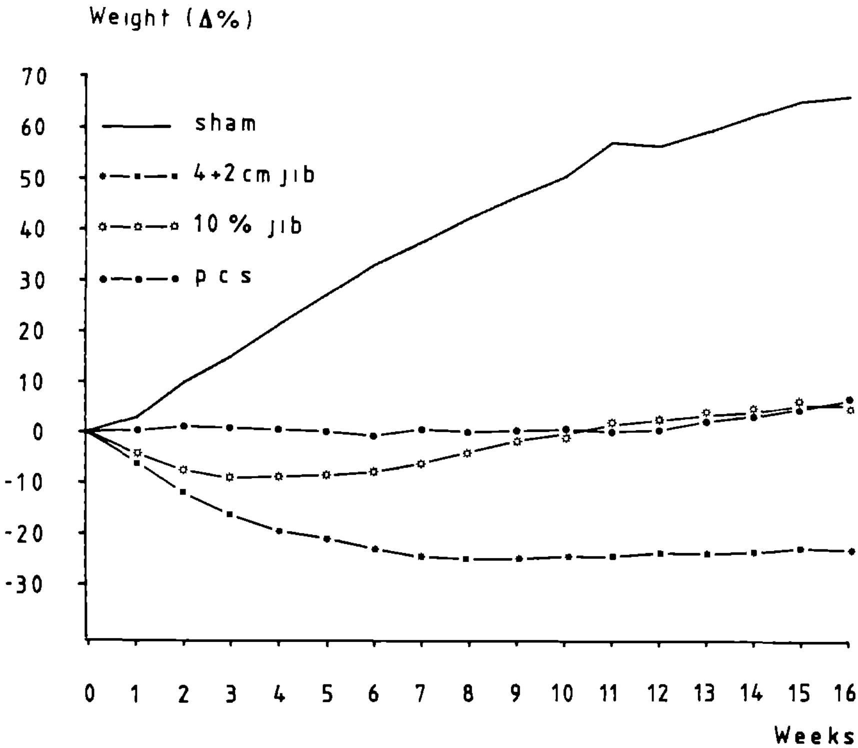

Fig. 4.1. Mean changes in body weight after 4 types of operation. Results are expressed as mean percentage gain or loss compared to preoperative weight.

weight-saving operations should not be evaluated from the difference between preoperative and postoperative weight within each group, but rather from the difference with the weight of the rats in the sham group 16 weeks after their operation.
This means that the actual loss of weight induced by the 4+2 cm shunt was 278 g (or 89% of preoperative weight).
Likewise, the 10% shunt resulted in a loss of weight of 169 g (or 60%) and the p.c. shunt in a loss of 166 g (or 60% of preoperative weight).
To evaluate the difference of change of weight between the first and last measurement after the operation among the 4 groups an analysis of covariance has been used followed by a simultaneous multiple comparison method according to Scheffé.
In this analysis the change of weight has been adjusted for differences of body length, small intestinal length and age among the four groups by introducing them as covariables.
It appears then that the 4+2 cm rats lose weight very significantly as compared to the sham rats ($p < 0.001$). Also the gain of weight of the 10% group and the p.c.s. group is significantly less than in the sham rats ($p < 0.001$) and significantly more than in the 4+2 cm group ($p < 0.001$). However, the gain of weight in the 10% group is not significantly different from the p.c.s. group ($p > 0.10$).

4.7.4 Discussion

Table 4.10 shows that the preoperative weights of the 122-days-old animals used in the present study are similar to those found by de Waard (1978) but differ considerably with those reported by Zucker (1961) and Powley (1976).

	Zucker 1961	*Powley 1976*	*de Waard 1978*	*Cremers 1982*
fatty male	*580*	*590*	*400*	*384*
fatty female	*480*	*490*	---	*328*
lean male	*390*	*380*	*280*	*292*

Table 4.10 Weight (in grams) of Zucker rats with a mean age of about 125 days as reported in various studies.

This difference, which cannot be explained by the fat content of the rat chow given, illustrates the difficulty in comparing the quantitative results of the various studies performed with fatty rats.
Several authors have published results of jejunoileal bypass in fatty rats. Grosfeld (1977) found a loss of weight of 18% of preoperative body weight, 4 weeks after a 90% jejunoileal bypass in Zucker rats (weight ± 500 g).
Baggio et al. (1976) report the effect of a 4+2 cm end-to-end jejunoileal bypass in Sprague-Dawley rats fattened with insu-

lin. This operation, which bypasses 95% of the small intestine, induces a loss of weight of 26% of preoperative body weight within 40 days. Similar results were found by Sclafani (1978) for both VMH rats (made hyperphagic by a ventro-medial hypothalamic knife cut) and Zucker rats, and by Kissileff (1979) for Zucker rats. These data compare reasonably well with those found in our study. In particular the course of the weight curve always seems to be identical.

Backman (1975) has divided the typical weight curve found after jejunoileal bypass in man into five periods (cf. also Juhl, 1974, and Halverson, 1978, 1980).

During the first period of about 3 weeks the patient loses weight rapidly. The second period is characterized by a steady, linear loss of weight, while during the third period the loss of weight levels off towards the maximal degree of loss of weight. The fourth period shows some gain, probably induced by intestinal adaptation, and in the fifth period a steady state is reached with fluctuations of a few kilograms. These five periods are not so clearly seen in our 10% group but the 4+2 cm group shows a nearly similar picture (fig. 4.1). However, the fact that the animals are still growing when subjected to the bypass procedure, as the sham group shows, makes any comparison with patients difficult and speculative.

For the same reason, the actual weight-losing effect of the various operations can only be evaluated by comparison with the sham-operated controls and not by a comparison of pre- and postoperative weight in a single group. Thus, a 7% shunt (4+2 cm) leads to an actual loss of weight of 89% and a 10% jejunoileal bypass to a loss of 60% of body weight.

It is remarkable that the portacaval shunt has nearly the same effect as the 10% bypass, inducing a loss of weight of 60%. So apart from a considerable reduction of absorptive intestinal surface another mechanism must be present. It apppears that decrease in food intake is a major contributing factor as Grosfeld (1977) shows in Zucker rats following jejunoileal bypass (a food reduction of ± 23%) and Pector (1981) shows in Zucker rats following portacaval shunt (a food reduction of 40%-60%).

The same significant influence of food reduction is demonstrated by Sclafani (1978) in VMH-bypassed rats and fat Zucker rats and by Kissileff (1979) in fat Zucker rats.

4.8 The change in body weight after 16 weeks adjusting for sex, shunt length, age, length of small intestine and body weight at operation

4.8.1 Correlation between change of body weight and length of the shunt

The Pearson correlation (= r) between change of body weight (between the first and last measurement after operation) and length of the shunt as percentage of the length of the small intestine is significantly positive in the composed 4+2 cm and 10% group ($r = 0.61$, $p < 0.001$).

Thus a comparatively longer shunt, leaving a larger part of the functional intestine, causes a smaller decrease in weight.

4.8.2 Multiple regression model

Apart from the percentage of the shunt which affects change of weight, other parameters can be thought of which possibly influence weight change e.g. sex, length of the body, small intestinal length, weight and age at operation.
For purposes of adjustment of these parameters a multiple regression model has been made use of.
Again a significantly positive ($p < 0.001$) relation between change of weight and length of the shunt is found.
Examination of the relation between weight change and each of the parameters mentioned above (body length, weight, age, sex and small intestinal length), under the latter model only gives a significant result for the length of the small intestine ($p = 0.02$).
Thus, generally speaking, the longer the small intestine, the lesser the ultimate decrease in weight.

4.8.3 Predictive equation

The multiple regression model used above gives rise to the following predictive equation:

$$\Delta W = 8.8 + 35\ Y1 - 0.68\ Y2 + 0.30\ Y3 - 2.0\ Y4 - 0.23\ Y5 - 15\ Y6$$

in which,

ΔW = change of weight in g after 16 weeks,
Y1 = length of shunt as percentage of total small intestinal length,
Y2 = age in days on day of operation,
Y3 = small intestinal length in mm on day of operation,
Y4 = length of the body in mm on day of operation,
Y5 = weight in g and on day of operation,
Y6 = sex (1 = male, 2 = female).

This equation estimates the relation between the loss of weight, as measured 16 weeks after the construction of an end-to-end jejunoileal bypass in Zucker rats, and several characteristics on day of operation.
In this model the least significant variable is sex.
The model thus can be simplified by omitting the influence of sex. If we then examine the relation between change of weight and each of the remaining variables under a reduced model, it appears that weight reduction is hardly affected ($p > 0.10$) by body weight at operation. When we again reduce the model by also omitting the variable body weight at operation, all remaining variables, viz. percentage of shunt, length of body, length of small intestine and age, each have a significant contribution to make (respectively $p < 0.001$, 0.05, 0.02 and 0.05).
Thus, in sequence of importance, change of weight 16 weeks after jejunoileal bypass is affected by length of the shunt, length of the small intestine, length of the body and age at operation.
This equation underlines the importance of minutely measuring

the length of the shunt and the length of the small intestine. If one dares to transfer the result of this experiment in Zucker rats to the treatment of morbidly obese patients by jejunoileal bypass, one might conclude that each morbidly obese patient should have "his own" length of functioning intestine in jejunoileal bypass. This length of functioning intestine should be 10% of the length of the small intestine which is different in each patient. However, most patients are treated with a bypass in which the length of the functioning segment is a fixed length, e.g. 14-4 inches. Therefore, the length of the functioning segment is not related to the total small intestinal length. This may explain the wide range of loss of weight after jejunoileal bypass.

4.8.4 Conclusion

The most decisive factor determining loss of weight after jejunoileal bypass is the length of the functioning segment as percentage of the total small intestinal length.

EFFECT OF OPERATION ON SOME BIOCHEMICAL PARAMETERS IN BLOOD

5.1 Introduction

This chapter includes results of biochemical assays on blood samples, collected preoperatively and 7 weeks and 16 weeks postoperatively in the 4 experimental groups.
Since the rat has a limited circulating volume, drawing too much blood might cause anemia .Therefore only a small number of serum tests could be performed.
Hemoglobin was decided upon as a general parameter and bilirubin, glutamate-pyruvate transaminase (G.P.T., or alanine aminotransferase: A.L.A.T.) and alkaline phosphatase (A.P.) were chosen as parameters for liver degeneration which is a very serious complication of jejunoileal bypass; cholesterol and triglycerides were measured as parameters for lipid metabolism.
Regrettably, evaluation of electrolytes, renal function, calcium and phosphate, vitamins etc., had to be omitted.
Weight plots for Wistar rats in the pilot study showed a dip after 4 weeks (s.d. = 1.2 weeks).
In this period the influence on blood parameters by jejunoileal bypass is expected to be strongest.
Weight plots for Zucker rats however present a different picture as can be seen in 4.7.2.
As the aim was to evaluate blood parameters at the dip in the weight curve, blood samples were drawn around this period.
For all groups the mean period between operation and blood sampling was 51 days (s.d. = 20 days).

5.2 Methods

All blood samples were tested in the Clinical Chemical Laboratory for Pediatrics and Surgery of the St. Radboud Hospital, University of Nijmegen, The Netherlands, (Head: Dr. P.J.J.van Munster).
Plasma hemoglobin was measured according to van Kampen en Zijlstra (1961). Plasma bilirubin was measured according to Deenstra (1952), based on Jendrassik and Grof (1938). Plasma G.P.T. (= A.L.A.T.) was measured through an enzymatic method (Boehringer, Mannheim : Automated Analysis).
Serum Alkaline Phosphatase was measured according to Bessey, as modified by de Vries (1956). Serum cholesterol was measured through a stabilised Lieberman-Burchard method according to Ness, Patewka and Peacock (1964).
Serum triglycerides were measured through an enzymatic method (Boehringer, Mannheim: Triglycerides fully enzymatic). This assay is based on a modification according to Wahlefeld (1974).

5.3 Hemoglobin

5.3.1 Hemoglobin preoperatively

In table 5.1 the mean preoperative value of hemoglobin in serum is presented in the 4 experimental groups, both for male and female rats.

	Hb	sham	4+2cm	10%	p.c.s.
male	mean	10.1	9.6	9.7	8.6
	S.D.	0.3	0.8	0.6	0.4
	N	4	10	10	5
female	mean	9.8	9.4	9.7	8.8
	S.D.	0.8	0.6	0.4	0.5
	N	6	10	13	4

Table 5.1 Hb preoperatively (in mmol/l) for male and female Zucker rats in 4 experimental groups. N is number of rats.

According to a two-way analysis of variance no significant effects of sex (main effect and interaction effect) are to be found. However, the hypothesis that averaged over both sexes the 4 experimental groups have the same mean preoperative Hb, has to be rejected. A simultaneous multiple method of comparison according to Scheffé, reveals that this is mainly caused by the fact that the mean Hb in the p.c.shunt group is significantly lower than in the other 3 groups ($p \leq 0.01$). This might be explained by the higher age of this group (cf. 4.3.1). There is no significant difference in preoperative Hb-level among the other three experimental groups (cf. also table 5.2).

5.3.2 Postoperative changes in hemoglobin

Since no significant difference in preoperative Hb between sexes was found in the 4 groups (5.3.1), further data on Hb will be presented for groups as a whole; however, in the two-way analyses of variance used below the effect of sex is always implied.
Table 5.2 shows the mean values of hemoglobin, preoperatively and 7 weeks and 16 weeks postoperatively.

Hb	preoperatively (N)	after 7 weeks (N)	after 16 weeks (N)
sham	9.9 ± 0.6 (10)	10.1 ± 0.4 (9)	9.8 ± 0.9 (10)
4+2 cm	9.5 ± 0.7 (20)	8.3 ± 1.0 (19)	9.1 ± 0.7 (19)
10%	9.7 ± 0.5 (23)	9.1 ± 0.6 (22)	9.4 ± 0.9 (23)
p.c.s.	8.7 ± 0.4 (9)	9.9 ± 0.6 (10)	9.4 ± 0.5 (10)

Table 5.2 Effect of operation on hemoglobin. Results are given (in mmol/l) as average value plus or minus s.d.. N is number of rats.

According to Student's paired tests a sham operation does not affect plasma hemoglobin, neither after 7 weeks nor after 16 weeks ($p > 0.10$). When we compare the differences between preoperative Hb and Hb after 7 weeks for the 4 groups by a two-way analysis of variance, we find a significant result ($p < 0.001$). According to the method of Scheffé hemoglobin, as measured 7 weeks after a 4+2 cm jejunoileal bypass, is lowered significantly in comparison with the sham group ($p = 0.01$). A similar effect, though to a lesser extent and not significant, is observed after a 10% bypass. With an analogous analysis we do not find any significant differences between the 4+2 cm or 10% group and the sham group with respect to the change in hemoglobin after 16 weeks (the overall analysis of variance gives a $p = 0.08$). The Hb-levels have again risen almost to the preoperative value.
So a 4+2 cm jejunoileal bypass induces a decrease of hemoglobin at the time of the lowest weight (actually 9 weeks postoperatively, cf. 4.7.2) whereas after adaptation of the functioning intestine (cf. chapter 6) the level of hemoglobin is unaffected.
The rise in hemoglobin after portacaval shunt is difficult to evaluate because of the significantly lower preoperative level, possibly originating from the higher age in this group. However, the rise in hemoglobin, as measured after 7 weeks and after 16 weeks, is not significant in comparison with the sham group according to Scheffé.

5.3.3 Hemoglobin in male lean Zucker rats

Mean hemoglobin in 4 male lean Zucker rats was 9.3 in mmol/l (s.d. = 1.0 mmol/l).

5.4 Serum bilirubin

Bilirubin was assayed in serum preoperatively and 7 and 16 weeks postoperatively.
With the exception of one rat (in the sham group), which showed a certain degree of liver degeneration (bilirubin: 127 mmol/l, G.P.T.: 33 U/l, A.P.: 157 U/l), all bilirubin values measured fell into the normal range. Thus, neither the jejunoileal bypass operations nor the portacaval shunt affect the bilirubin concentration. This does not necessarily mean that liver function is unimpaired; bilirubin might simply be too aspecific a parameter in our experiment.

5.5 Serum glutamate-pyruvate transaminase

5.5.1 Serum glutamate-pyruvate transaminase preoperatively

In table 5.3 the mean preoperative values for G.P.T. in serum are presented for the 4 experimental groups, both for male and female rats.
It is obvious that comparison of the four groups is impaired by the great variation in G.P.T. levels, in particular in the 4+2 cm and 10% shunt groups.
Statistical evaluation by means of a two-way analysis of variance shows no significant differences, neither among the groups nor between the sexes.

G.P.T.	sham	4+2 cm	10%	p.c.s.
male	47	123	54	47
S.D.	15	239	55	23
N	4	10	10	5
female	32	120	93	92
S.D.	8	102	76	36
N	6	9	13	5

Table 5.3 Mean G.P.T. preoperatively (in U/l) for male and female Zucker rats in 4 experimental groups. N is number of rats.

5.5.2 Postoperative changes in serum glutamate-pyruvate transaminase

Table 5.4 compares the mean values of G.P.T. with those measured 7 and 16 weeks postoperatively, without differentiation into sexes.

G.P.T.	preoperatively (N)		after 7 weeks (N)		after 16 weeks (N)	
sham	38 ± 14	(9)	33 ± 10	(9)	40 ± 25	(7)
4+2cm	122 ± 182	(19)	31 ± 8	(18)	33 ± 8	(19)
10%	71 ± 67	(22)	31 ± 15	(22)	33 ± 13	(22)
p.c.s.	70 ± 37	(10)	27 ± 5	(10)	22 ± 9	(10)

Table 5.4 Effect of operation on G.P.T. in serum. Results are expressed (in U/l) as mean value plus or minus s.d.. N is number of rats.

Clearly, none of the four types of operation induces an increase in serum G.P.T. level compared to the preoperative value. The variation in serum G.P.T., assayed 7 and 16 weeks postoperatively, is much smaller than the unexpected high variation found preoperatively. Two-way analyses of variance (with factors operation and sex) of the changes between pre- and postoperative values after 7 weeks and after 16 weeks show no significant difference in serum G.P.T., among the four experimental groups. This might be due to the considerable variation of the values. Anyway, liver function, as monitored by the level of serum G.P.T., is not found to deteriorate after jejunoileal bypass or portacaval shunt in Zucker rats, at least not within the first 16 weeks.

5.5.3 Serum glutamate-pyruvate transaminase in male lean littermates

The average G.P.T. level of 4 male lean littermates was 18 ± 2 (s.d.) U/l.
This figure seems to be lower than that found in fat male Zucker rats of the same age. It should be compared with fat male rats in the 10% group (54 U/l) or p.c.s. group: 47 U/l (see table 5.3).
This higher value of serum G.P.T. might be an expression of the fatty liver degeneration in fatty Zucker rats (see chapter 7, Hepatic histology).

5.6 Alkaline Phosphatase in serum

5.6.1 Alkaline Phosphatase preoperatively

In table 5.5 the mean preoperative values of A.P. in serum are given for the 4 experimental groups.

A.P.	*sham*	*4+2 cm*	*10%*	*p.c.s.*
male	*174*	*175*	*169*	*127*
S.D.	*24*	*64*	*61*	*15*
N	*4*	*10*	*10*	*5*
female	*120*	*156*	*162*	*133*
S.D.	*39*	*59*	*69*	*54*
N	*6*	*10*	*13*	*5*

Table 5.5 Mean preoperative Alkaline Phosphatase (in U/l) in male and female Zucker rats. N is number of rats.

Two-way analysis of variance shows no significant differences neither between sexes nor among groups.

5.6.2 Postoperative changes in Alkaline Phosphatase

Postoperative levels of A.P. , measured after 7 and 16 weeks, are compared with the preoperative concentrations in table 5.6, where differentiation in sexes is omitted.

A. P.	*preoperatively (N)*	*after 7 weeks (N)*	*after 16 weeks (N)*
sham	*142 ± 43 (10)*	*101 ± 40 (10)*	*89 ± 19 (10)*
4+2 cm	*165 ± 60 (20)*	*176 ± 43 (19)*	*145 ± 37 (20)*
10%	*165 ± 64 (23)*	*154 ± 48 (22)*	*125 ± 38 (23)*
p.c.s.	*130 ± 41 (10)*	*66 ± 27 (10)*	*88 ± 14 (10)*

Table 5.6 Average level of Alkaline Phosphatase (in U/l), preoperatively and 7 and 16 weeks postoperatively. N is number of rats.

Through separate Student's paired tests we find significant decreases after 7 and 16 weeks for all groups except the 4+2 cm group and the 10% group after 7 weeks.
The differences in changes of the serum Alkaline Phosphatase between preoperative and postoperative values were further evaluated with a two-way analysis of variance (with factors operation and sex) followed by a simultaneous multiple comparison method according to Scheffé. The hypothesis of equal changes after 7 weeks for the 4 groups, averaged over both sexes, has to be rejected ($p = 0.01$). The slight increase in A.P. , measured after 7 weeks in the 4+2 cm bypass group, and the decrease, measured after 7 weeks in the portacaval shunt group, are significantly different ($p = 0.03$).
After 16 weeks no significantly different changes are found.

5.6.3 Alkaline Phosphatase in male lean Zucker rats

The average level of A.P. in 4 male lean littermates was 90 ± 16 (s.d) U/l. This value for lean littermates should be compared with the male fatty Zucker rats in table 5.5 .
As for G.P.T. (5.5.3) this higher value of A.P. might be an expression of the fatty degeneration of the liver in fatty Zucker rats (see chapter 7, Hepatic histology).

5.7 Cholesterol in serum

5.7.1 Cholesterol preoperatively

The mean preoperative concentrations of cholesterol in serum of male and female rats are given in table 5.7 .

cholesterol	*sham*	*4+2 cm*	*10%*	*p.c.s.*
male	*4.45*	*4.22*	*4.09*	*3.96*
S.D.	*0.98*	*0.50*	*0.43*	*0.72*
N	*4*	*9*	*8*	*5*
female	*3.42*	*4.20*	*3.96*	*5.08*
S.D.	*1.15*	*1.03*	*1.27*	*1.53*
N	*3*	*8*	*12*	*5*

Table 5.7 Mean preoperative serum cholesterol (in mmol/l) in 4 experimental groups. N is number of rats.

Two-way analysis of variance shows no significant differences neither between sexes nor among any of the groups.

5.7.2 Postoperative changes in cholesterol

Table 5.8 shows mean values of cholesterol preoperatively and 7 and 16 weeks after operation without differentiation into sexes.
According to separate Student's paired tests the level of cholesterol has not changed significantly 7 weeks after operation in any of the experimental groups ($p > 0.05$).

chol.	preop.	(N)	7 weeks	(N)	16 weeks	(N)
sham	4.01 ± 1.11	(7)	4.36 ± 1.96	(7)	4.45 ± 1.64	(8)
4+2 cm	4.17 ± 0.81	(15)	3.83 ± 0.73	(15)	3.76 ± 0.91	(15)
10%	4.01 ± 1.01	(20)	3.62 ± 0.73	(20)	3.85 ± 0.74	(17)
p.c.s.	4.52 ± 1.27	(10)	3.53 ± 0.62	(9)	3.30 ± 0.46	(10)

Table 5.8 Effect of operation on serum cholesterol. Results are expressed (mmol/l) as mean value plus or minus s.d. for whole groups without differentiation into sexes. N is number of rats.

Comparing the preoperative values with those measured 16 weeks after operation, we notice that no significant changes have occurred in either sham or 10% bypass group. However, both the 4+2 cm bypass ($p = 0.02$) and the portacaval shunt group ($p = 0.009$) show a significant decrease in cholesterol.
These data apply to groups treated as a whole, including both female and male rats. However, pronounced differences between both sexes appear to exist with respect to the changes in level of cholesterol after 7 weeks and after 16 weeks (table 5.9).

Δ cholesterol	sham (N)	4+2 cm (N)	10% (N)	p.c.s. (N)
male 7 w	1.10 (4)	-0.48 (8)	-0.39 (8)	-0.10 (5)
	± 1.42	± 0.51	± 0.76	± 0.75
16 w	1.35 (4)	-1.06 (7)	-0.19 (6)	-0.58 (5)
	± 0.72	± 0.65	± 0.49	± 0.43
female 7 w	-0.64 (3)	-0.19 (7)	-0.39 (12)	-1.63 (4)
	± 1.07	± 1.09	± 1.39	± 1.28
16 w	-0.93 (2)	-0.07 (8)	-0.19 (11)	-1.86 (5)
	± 1.09	± 0.68	± 0.62	± 1.37

Table 5.9 Changes (= Δ) in serum cholesterol, as measured 7 and 16 weeks after operation. For each experimental group separate values are given for male and female rats. Results are expressed as average change plus or minus s.d. in mmol/l, comparing preoperative values with those measured 7 and 16 weeks postoperatively. Between brackets the number of rats has been given.

According to a two-way analysis of variance averaged over the 4 groups the mean decrease for the female rats differs significantly from the slight mean change for the male rats, both after 7 weeks ($p = 0.03$) and after 16 weeks ($p = 0.01$). The hypothesis that after 7 weeks averaged over both sexes the mean changes for the 4 groups are equal cannot be rejected ($p > 0.10$). However, there is an indication that this is not true for both sexes taken separately; the interaction test results in a p-value equal to 0.08 and we observe large differences in change between the sham group and the portacaval shunt group both for male and female rats. The male sham rats even show some increase.
After 16 weeks the mean changes for the 4 groups averaged over both sexes are not equal ($p = 0.002$). According to the method of Scheffé this is mainly caused by a larger decrease for the portacaval shunt group in comparison with the sham group ($p = 0.01$) and the 10% group ($p = 0.02$).
Neither the 4+2cm bypass nor the 10% bypass induces a lowering of serum cholesterol which is significantly different from the effect induced by a sham operation. The interaction test of the two-way analysis of variance shows a clear difference between both sexes for the mean changes ($p < 0.001$) after 16 weeks.

5.7.3 Cholesterol in male lean Zucker rats

Serum cholesterol in 4 male lean littermates was 3.10 ± 0.40 (s.d.) mmol/l .
This level seems to be lower than those measured in male sham (4.45 ± 0.98 mmol/l) and male p.c.shunt (3.96 ± 0.72 mmol/l) rats, which at time of assay were nearest in age.
The male rats in the portacaval shunt group, with a decreased cholesterol of 3.38 mmol/l after 16 weeks, approximate cholesterol of the lean littermates (3.1 mmol/l).
The same applies to the 4+2 cm group (3.16 mmol/l) and, to a lesser extent, to the 10% group (3.9 mmol/l). (cf. table 5.7 and 5.9).

5.7.4 Discussion

The fat Zucker rat is characterized by a moderate but significant hypercholesterolemia in comparison with its lean littermate (Zucker, 1962, 1965; Barry and Bray, 1969; Bray, 1977; Bach, 1977; Comai, 1978; de Waard, 1978; Pector, 1981; also this thesis cf. 5.7.1 and 5.7.3).
The values for cholesterol in the present experiment (table 5.8) are similar to those reported by Barry (1978) and de Waard (1978). Barry measured in fat female Zucker rats, respectively 4 and 9 months old, serum cholesterol levels of 4.09 and 4.86 mmol/l. De Waard found in male fat Zucker rats a steady increase in serum cholesterol, up to 3.96 mmol/l at the age of 20 weeks. These levels are considerably lower than those reported by Zucker (1962) who measured in 6-week-old male fat Zucker rats a level of 3.78 mmol/l. At the age of 12 weeks cholesterol was increased to 8.54 mmol/l and between 6 and 12 months the cholesterol concentration was approximately 9.6 mmol/l.
These differences are possibly due to a different fat content

of several diets as studied by Malewiak (1977), de Waard (1978) and Comai (1978).
One of the positive effects of jejunoileal bypass in morbidly obese patients, with or without hyperlipidemia (type IIa or type IV according to Fredrickson, 1978), is a marked and permanent reduction of plasma cholesterol and triglycerides (Buchwald, 1981; Ackerman, 1982).
We have found a significant decrease in serum cholesterol 16 weeks after a 4+2 cm jejunoileal bypass (13% decrease) and a small non-significant decrease 16 weeks after a 10% jejuno-ileal bypass (2% decrease) provided we neglect the different behaviour of both sexes (cf. table 5.8). However, both decreases did not differ significantly from the change in the sham group.
Grosfeld (1977) reported that hepatic cholesterol levels were not affected by jejunoileal bypass in fat Zucker rats, while hepatic cholesterol synthesis was significantly increased. This excess synthesis of hepatic cholesterol results in supersaturation of bile which becomes cholelithogenic, thus possibly explaining in part the increased incidence of gallstones observed after jejunoileal bypass in patients.
Grosfeld does not mention serum cholesterol.
So our finding that serum cholesterol does not change significantly after jejunoileal bypass as compared to sham rats does not give any information about what is actually happening in cholesterol metabolism after jejunoileal bypass.
In our experiment portacaval shunt lowered serum cholesterol significantly. Besides, this decrease differs significantly from the change in the sham group. Sixteen weeks postoperatively the concentration was 26% lower than the concentration of the sham rats. This phenomenon has also been described by Pector (1981) who reported that after portacaval shunt in lean and fatty Zucker rats the concentration of liver lipids, including cholesterol, remained unaffected, while hypercholesterolemia and the in vivo incorporation of $3H2O$ (tritiated water) into total liver cholesterol decreased by 43%.

5.8 Triglycerides

5.8.1 Triglycerides preoperatively
The mean preoperative serum triglyceride levels in male and female rats are given in table 5.10 .

triglycerides	sham	4+2 cm	10%	p.c.s.
male	5.49	3.81	4.18	4.51
S.D.	2.79	1.83	1.65	1.86
N	4	9	8	5
female	6.27	5.59	4.73	7.58
S.D.	3.24	1.88	1.00	5.58
N	6	10	13	5

Table 5.10 Mean preoperative serum triglyceride (in mmol/l) in 4 experimental groups. N is number of rats.

Two-way analysis of variance shows significantly elevated triglyceride levels in serum of female rats as compared to male rats (with 6.04 and 4.50 mmol/l as estimates of the means respectively; $p = 0.02$).
There is no significant difference in average triglyceride concentration among the four groups averaged over both sexes.

5.8.2 Postoperative changes in triglyceride

Both after 7 weeks and after 16 weeks mean triglyceride levels in female rats are higher than in male rats according to a two-way analysis of variance but this fact does not essentially influence the overall change in triglycerides in the experimental groups. Therefore table 5.11 gives the postoperative values without taking into account the male-female difference.

triglyc.	*preop.*	*(N)*	*after 7 w*	*(N)*	*after 16 w*	*(N)*
sham	*5.96 ± 2.93*	*(10)*	*6.23 ± 2.57*	*(10)*	*5.88 ± 2.57*	*(9)*
4+2 cm	*4.75 ± 2.02*	*(19)*	*0.89 ± 0.52*	*(19)*	*1.29 ± 0.56*	*(19)*
10%	*4.52 ± 1.28*	*(21)*	*1.90 ± 1.54*	*(22)*	*2.76 ± 1.35*	*(22)*
p.c.s.	*6.04 ± 4.24*	*(10)*	*2.70 ± 0.60*	*(10)*	*3.48 ± 1.65*	*(10)*

Table 5.11 Effect of operation on serum triglycerides. Results are expressed (mmol/l) as mean value plus or minus s.d. without sex differentiation. N is number of rats.

Separate Student's paired tests give highly significant decreases after 7 weeks and after 16 weeks for the 4+2 cm group and 10% group ($p < 0.001$), significant decrease for the p.c. shunt group after 7 weeks ($p = 0.031$) and nearly significant decrease ($p = 0.084$) after 16 weeks. No significant differences are found for the sham group.
A two-way analysis of variance shows that sex does not affect changes in triglycerides between values measured 7 weeks or 16 weeks after operation and preoperative concentrations. Averaged over both sexes the overall hypothesis of equal changes after 7 weeks or after 16 weeks has to be rejected ($p < 0.001$ and $p = 0.05$ respectively). According to the simultaneous comparison method of Scheffé this has been caused by the following differences.
Rats with a 4+2 cm jejunoileal bypass show a significantly larger reduction in triglycerides after 7 weeks in comparison with sham rats ($p = 0.001$). Further, rats with a 10% jejunoileal bypass and rats with a portacaval shunt show a significantly larger reduction in triglycerides after 7 weeks in comparison with sham rats ($p = 0.02$).
There exists no significant difference in triglyceride reduction, as measured after 7 weeks, between rats with a 4+2 cm bypass and rats with a 10% bypass.
After 16 weeks only rats with a 4+2 cm jejunoileal bypass show an almost significantly larger reduction in triglycerides in comparison with sham rats ($p = 0.09$).

5.8.3 Triglycerides in male lean Zucker rats

Serum triglycerides in 4 male lean littermates are 0.77 ± 0.18 mmol/l (mean ± s.d.).
Only serum triglyceride levels in fat rats with a 4+2 cm jejunoileal bypass, as measured 7 weeks postoperatively, approximate those found in lean rats (cf. table 5.11). However, their triglyceride level has significantly increased again to 1.29 mmol/l 16 weeks after operation (Student's paired test: $p < 0.001$). This increase may be due to adaptation of functional intestine.

5.8.4 Discussion

The fat Zucker rat is characterized by a substantial increase of serum triglycerides in comparison with its lean littermates (see 2.3.4).
Zucker (1965) reported that serum triglycerides increase with age.
Barry (1969) found a decrease in triglyceride level when comparing rats of 4 and 9 months old. Serum triglycerides in female fatty Zucker rats, aged 4 months, were 8.78 ± 0.23 mmol/l (mean and S.E.M.) and at the age of 9 months were 4.41 ± 1.86 mmol/l (mean and S.E.M.).
De Waard (1978) reported an increase of triglycerides for male Zucker rats up to 5.59 ± 0.58 mmol/l (mean and S.E.M.) at 14.5 weeks of age, followed by a decrease to 4.40 ± 0.64 mmol/l (mean and S.E.M.) at 20.5 weeks.
In our sham rats (age at operation 16 weeks) a slight and not significant increase of serum triglycerides is present after 7 weeks. Triglycerides after 7 weeks in male sham rats: 5.30 mmol/l (s.d. = 2.75 mmol/l), N = 4 ; in female sham rats: 6.85 mmol/l (s.d. = 2.49 mmol/l), N = 6.
In our sham rats a minimal and not significant decrease of serum triglycerides is found after 16 weeks. Triglycerides after 16 weeks in male sham rats are 5.20 mmol/l (s.d. = 1.65 mmol/l), N = 3 ; and in female rats 6.23 mmol/l (s.d. = 3.01 mmol/l), N = 6.
This means that Zucker rats probably show a maximum level of triglycerides when they are about 19 weeks old.
Comai (1978) reported serum triglycerides in male fat Zucker rats to be of a higher level than in female fat Zucker rats (4.20 and 3.93 mmol/l, respectively). We find a significant effect the other way round, not only preoperatively but also 7 and 16 weeks after operation averaged over all experimental groups. It is impossible to compare absolute triglyceride values found by the various authors due to differences in age of rats and method of triglyceride assay. Grosfeld (1977) demonstrates a significant 48% reduction in serum triglycerides 4 weeks after 90% jejunoileal bypass (comparable with our 10% bypass) in fat rats as compared to controls (1.67 ± 0.23 mmol/l and 3.21 ± 0.36 mmol/l, respectively). Lean rats had even lower triglycerides: 0.97 ± 0.18 mmol/l. Our results are similar, especially 7 weeks postoperatively with an 86% reduction of triglycerides in the 4+2 cm jejunoileal bypass group and a 70% reduction in the 10% jejunoileal bypass group as compared to the sham rats. The reduction after 16 weeks is 78% and 53% respectively. This probably means that between 7

weeks and 16 weeks a certain degree of adaptation in intestinal absorption occurs, as is also indicated by the weight curves (cf. 4.7.2 and 4.7.3).
The results of the p.c.shunt group are in agreement with those reported by Pector (1981) who found in male fatty Zucker rats 3 weeks after portacaval shunt a reduction of 78% of triacylglycerol, if compared with sham rats fed ad libitum. Our experiments show a 57% reduction of triglyceride 7 weeks after portacaval shunt and a 41% reduction 16 weeks after portacaval shunt as compared with sham rats.
Again, as in jejunoileal bypass, a certain adaptation to the shunt appears to occur.

5.9 Summary

Blood samples have been assayed biochemically, preoperatively and 7 and 16 weeks postoperatively, in the four experimental groups. Bilirubin, G.P.T. and A.P. were chosen as parameters for liver degeneration. Cholesterol and triglycerides were measured as parameters for lipid metabolism.
Hemoglobin was lowered 7 weeks after a 4+2 cm bypass but after 16 weeks there was no significant difference with preoperative values in any of the groups.
None of the parameters chosen to monitor possible liver degeneration, did show any consistent increase after operation. In fact, average G.P.T. and A.P. activities measured 16 weeks after 4+2 cm bypass, 10% bypass or portacaval shunt, were all lower than activities measured preoperatively. Thus, our data suggest that no liver damage occurs within the first 16 weeks after jejunoileal bypass or portacaval shunt in the fat Zucker rat.
Both jejunoileal bypass and portacaval shunt strongly affect the level of triglycerides in serum. Sixteen weeks after a 4+2 cm bypass or a 10% bypass a significant reduction in triglycerides is found. It appears that there exist pronounced differences in serum triglycerides between male and female rats.
After 16 weeks a 4+2 cm jejunoileal bypass significantly lowers the level of cholesterol in the serum compared to the preoperative value. However, this decrease is not significant in comparison with the change of the level of cholesterol in sham rats 16 weeks after operation.

MORPHOLOGICAL CHANGES IN THE SMALL INTESTINE AFTER A SHAM OPERATION , JEJUNOILEAL BYPASS OR PORTACAVAL SHUNT

6.1 Introduction

This chapter deals with macroscopic and microscopic changes in jejunum and ileum which have been found 16 weeks after jejuno-ileal bypass or portacaval anastomosis .
A number of rats with a 4+2 cm jejunoileal bypass was sacrificed after one week or after two weeks, for the purpose of studying early effects.
It has been known for many years that diarrhea, often seen after massive resection of small bowel or jejunoileal bypass, diminishes with time. Some time after operation a substantial dilatation and elongation of the remaining intestine is seen.
This macroscopic adaptation reflects microscopic structural changes, in particular elongation of the villi in a thickened intestinal wall.
Whereas some animal experiments have shown this adaptation, similar studies in man are scarce.

6.2 Anatomy of the small intestine

In the rat the first part of the small intestine, the duodenum, forms a large semicircle and ends after being crossed by the transverse colon. It is suspended at this level by a ligament which corresponds to Treitz's ligament in man.
The jejunum, fairly short, begins at the level of this ligament, which thus fixes and enables one to identify the first loop.
Finally, the ileum forms the greater part of the small intestine, and, passing down to the cecum, becomes progressively smaller in diameter.
The whole of the intestine is attached to the posterior abdominal wall by a double layer of mesentery, containing blood and lymphatic vessels; the two layers are also separated in places by fatty tissue.
The jejunum and ileum are extremely mobile and thus do not have any constant relations (Lambert, 1965).
In man the boundary between jejunum and ileum is arbitrarily localized at two-fifths of the total length of the small intestine (Gardner,1966; Anson and McVay, 1971; Trier, 1978).
The walls of the jejunum and ileum, which are virtually identical in structure, consist of five coats: the mucosa (including muscularis mucosae),submucosa, circular muscularis, longitudinal muscularis and serosa.
The mucosa is characterized by marked plication, especially in the proximal jejunum; more distally the number of plicae

diminishes. These folds, known as plicae circulares or Kerckring's folds or valvulae conniventes ("closing valves"), are duplications of the mucosa and are kept together by the submucosa. The folds vary in height and some of them extend all the way around the internal circumference, while others make up only half or two-thirds of the circle or spiral around twice or more.
Projecting into the lumen they will to a certain extent slow down the progression of the luminal contents, but their essential function is certainly to increase the absorptive surface area.
The histological structure of the mucosa of the small intestine is accounted by for the presence of two main compartments. First, there is the functional absorptive compartment normally consisting of tall regular fingerlike villi, covered for the most part by absorptive epithelial cells or "enterocytes". Secondly, there is a basal compartment occupied largely by the crypts of Lieberkuhn.These are simple tubular glandlike structures, the luminal orifices of which are grouped around the bases of villi. Most of the cells lining the crypts are maturing or dividing enterocyte precursor cells or "enteroblasts" .
Forming the villous core and surrounding the crypts is the lamina (or tunica) propria mucosae, which consists mainly of supportive connective tissue elements, enclosing blood vessels,lymphatics, lymphoreticular cells and a variety of other leucocytes.The lamina propria is separated from the submucosa by a thin double-layered structure known as the lamina muscularis mucosae (Lee, 1980).
The muscularis mucosae, which separates the mucous membrane from the submucosal coat, is composed of two thin nonstriated muscle layers, which keep the movable mucosal layer in place.
The tunica submucosa is made up of collagen connective tissue, the fibers of which form a network of lozenge-shaped meshes.
By altering the angles of its meshes, this submucosal network is able to adapt itself to changes in the diameter and length of the intestinal lumen. The submucosa contains a rich network of capillaries and larger vessels, numerous lymphatics and the submucous nerve plexus of Meissner.
The muscularis propria is built up of smooth muscle cells. The thick inner circular layer and the thinner outer longitudinal layer are connected by convoluted transitional fascicles in the area where they border on each other. Between the two layers is spread a network of nonmyelinated nerve fibers and ganglion cells, the myenteric plexus of Auerbach.
The serosa is composed of a layer of flat, polygonal epithelia, and the subserosa of very loose connective tissue (Netter, 1962).
Most studies on hypertrophy and atrophy after jejunoileal bypass and resection of small intestine have been concerned with mucosal changes as substrate of adaptation while neglecting the other layers of the intestinal wall. We have examined, therefore, all layers.

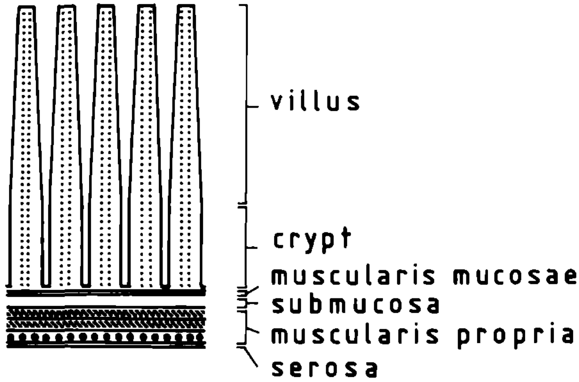

Fig. 6.1. Schematic anatomy of the small intestine of the fat Zucker rat.

Fig. 6.2. Jejunum of the fat Zucker rat at operation. (H.E.: x 26).

6.3 Methods

Sectioning and staining of specimens is described under 3.2.9 .
Transversal and longitudinal cross sections were examined with an eye-piece micrometer and height of the five tallest well-oriented villi and height (or depth) of their respective crypts , muscularis propria and thickness of the entire wall were measured in mu.
Villous height is taken as the distance between villous extremity and villous base, judged to be that point on the epithelial surface at which the villous epithelium curves on to the horizontal plane.
Crypt height is taken as the distance between the crypt base and the horizontal epithelial surface at the villous base (Lee, 1980).
For purposes of statistical analysis the mean of the 5 measurements in the circular preparations was taken unless, as in a few cases, the quality of the circular preparation was much less satisfactory than that of the longitudinal preparation. In practice the values obtained from either circular or longitudinal preparations did not differ much, at least if not measured at the anastomosis. This was also found by Fenyö (1976) although Nygaard (1967) found a local hypertrophy in the vicinity of the anastomosis both after transections and resections.
Once villous height, crypt height, muscularis propria thickness and total-wall thickness are known one can calculate the thickness of the mucosa and the submucosa.
The mucosa is the sum of villous height, crypt height and muscularis mucosae, which proved to be 10 mu, whereas the submucosa is calculated as the difference between the thickness of the entire wall and the sum of mucosa and muscularis propria (see fig.6.1).
Apart from these objective microscopic values gross macroscopic appearance of the functional and excluded segment of small intestine was evaluated 16 weeks postoperatively.

6.4 Macroscopic aspects

6.4.1 Hypertrophy of the functional segment and atrophy of the excluded segment 16 weeks after jejunoileal bypass

Macroscopic hypertrophy of the functional segment and macroscopic atrophy of the excluded segment were scored as absent, hardly present or clearly present when the rats were examined in anesthesia and sacrificed 16 weeks after operation.
Macroscopic hypertrophy of the intestine points to a clearly visible dilatation and elongation.
Macroscopic atrophy of the intestine points to a clearly visible reduction in diameter and length.
Macroscopic hypertrophy of the functional segment was always present in both jejunoileal bypass groups. In 93% of the cases (N = 43 rats) it was scored as clearly present (19 of 20 rats in the 4+2 cm group and 21 of 23 rats in the 10% group) and in 7% as hardly present (1 of 20 rats in the 4+2 cm group and 2

of 23 rats in the 10% group).
So the length of the functional segment, 7% or 10% respectively of the total small intestinal length after both types of bypass, seems not to affect the degree of macroscopic hypertrophy of the functional segment.
Macroscopic atrophy of the excluded segment was always present after jejunoileal bypass. In 84% of the cases (N = 43 rats) it was scored as clearly present (17 out of 20 rats in the 4+2 cm group and 19 out of 23 rats in the 10% group) and in 16% as hardly present (3 out of 20 rats in the 4+2 cm group and 4 out of 23 rats in the 10% group).
Again, the length of the functional segment, 7% or 10% respectively of the total small intestinal length, seems not to affect the degree of macroscopic atrophy of the excluded segment.

6.4.2 Hypertrophy of the functional segment and atrophy of the excluded segment one week or 2 weeks after jejunoileal bypass

Gross macroscopic appearance was evaluated in 5 male fatty Zucker rats with a 4+2 cm jejunoileal bypass, killed after one week, and in 7 male fatty Zucker rats with a 4+2 cm jejunoileal bypass , killed after 2 weeks.
After one week macroscopic hypertrophy of the functional segment was not yet visible in any of the rats. After two weeks early signs of macroscopic hypertrophy of the functional segment were found in 5 rats . At this stage hypertrophy was scored as clearly present in one rat.
The probability of occurrence of hypertrophy is significantly greater after two weeks than after one week ($p = 0.02$, Hemelrijk's two-sided test).
After one week macroscopic atrophy of the excluded segment was not yet visible in 2 rats and was scored as hardly present in 3 rats . After two weeks macroscopic atrophy of the excluded segment was hardly present in 6 rats and not yet present in 1 rat.
The probability of occurrence of atrophy after two weeks is not significantly greater than after one week ($p > 0.10$, Hemelrijk's two-sided test).
The conclusion of these observations is that macroscopic hypertrophy of the functional segment and macroscopic atrophy of the excluded segment already seem to occur between one and two weeks after 4+2 cm jejunoileal bypass.

6.5 Jejunum

6.5.1 Microscopic examination of jejunum at operation

Biopsies of proximal jejunum were taken from all rats of the 4 experimental groups, and from a group of fatty male Zucker rats with a 4+2 cm jejunoileal bypass killed after one week or after two weeks (biopsy 1a in fig.6.3).
Thus we have 4 experimental groups with a subdivision of the 4+2 cm jejunoileal bypass group regarding the period after operation, 1 week, 2 weeks and 16 weeks, respectively.
Table 6.1 gives villous and crypt height, thickness of muscularis propria and thickness of the entire wall of jejunum at operation in all male and female rats that were sacrificed

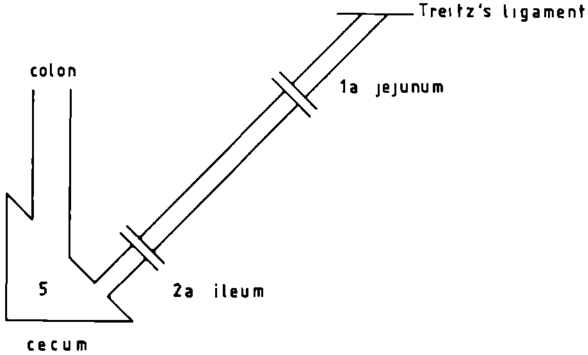

Fig. 6.3. Schematic anatomy of biopsies at operation in 4 types of operation.
Proximal jejunum (1a) and distal ileum (2a).

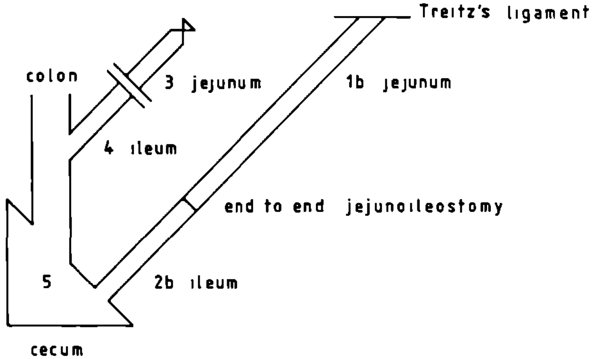

Fig. 6.4. Schematic anatomy of biopsies at autopsy after jejunoileal bypass.
Jejunal part of functional shunt (1b), ileal part of functional shunt (2b), proximal excluded jejunum (3), distal excluded ileum (4) and cecum (5).

after 16 weeks.

	N	villus	crypt	musc. prop	entire wall
male	29	525 ± 64	196 ± 25	91 ± 18	846 ± 61
female	34	513 ± 58	204 ± 24	93 ± 20	848 ± 71

Table 6.1 Microscopic parameters of the proximal jejunum at operation in male and female Zucker rats that were sacrificed after 16 weeks (mean and s.d. in μ).

The differences between sexes are not significant (Student's two sample test). Thus we may omit sex differentiation and compare the 4 experimental groups as a whole (table 6.2).

	N	villus	crypt	musc.prop.	entire wall
sham	10	520 ± 56	215 ± 17	96 ± 9	863 ± 64
4+2cm	20	514 ± 68	202 ± 26	96 ± 24	849 ± 70
10%	23	523 ± 66	195 ± 26	86 ± 16	842 ± 70
p.c.s.	10	513 ± 43	196 ± 19	95 ± 21	836 ± 54

Table 6.2 Microscopic parameters of the proximal jejunum in 4 experimental groups at operation (mean and s.d. in μ).

Villous height, crypt height, thickness of muscularis propria and thickness of entire wall of the proximal jejunum do not differ significantly among the 4 groups (analysis of variance).
If we are to compare the effects of the operations on the dynamic state of the intestinal mucosa the crypt height - villous height ratio is important. Villous height is in broad terms proportional to the enterocyte population; crypt height provides an estimate of the extent of generative epithelial activity and the ratio of crypt height to villous height is thought to be a function of enterocyte lifespan.
For man in the United Kingdom the crypt-villus ratio of jejunum should not exceed 0.6 (Lee, 1980).
For our 63 fatty Zucker rats the mean crypt-villus ratio of the jejunum at operation is 0.39.

<u>6.5.2 Proximal jejunum and jejunal part of functional segment 16 weeks after operation</u>
Villous height, crypt height, thickness of muscularis propria and thickness of entire wall are given in table 6.3 for the various experimental groups. Biopsies are taken from the proximal jejunum in the sham and p.c.shunt groups (biopsy 1a

in fig. 6.3) and from the jejunal part of the functional segment in the 4+2 cm and 10% bypass groups (biopsy 1b in fig. 6.4).

	N	villus	crypt	musc.prop.	entire wall
sham	10	560 ± 86	181 ± 25	107 ± 35	890 ± 98
4+2cm	20	571 ± 69	191 ± 29	102 ± 20	897 ± 107
10%	23	593 ± 86	203 ± 33	123 ± 34	958 ± 135
p.c.s.	10	506 ± 52	185 ± 21	115 ± 28	845 ± 93

Table 6.3 Microscopic parameters of proximal jejunum in sham and p.c.s. groups and of jejunal part of functional segment in 4+2 cm and 10% jejunoileal bypass 16 weeks after operation (mean and s.d.in μ).

When we compare tables 6.2 and 6.3 we find a minimal increase in thickness of the entire wall of proximal jejunum in the sham group (3%), a 6% increase in the 4+2 cm bypass group, a 14% increase in the 10% group and a negligible increase in the p.c.shunt group (1%). Separate Student's paired tests only show a significant increase for the 10% group ($p < 0.001$).
When we test the hypothesis that for all groups the total thickness changes in an equal way with a one-way analysis of variance, we find no clearly significant result ($p = 0.10$).
Comparing the 4 operation groups with a one-way analysis of variance we find a significant result with respect to change in crypt height ($p = 0.02$). According to the method of Scheffé this has mainly been caused by the fact that the observed increase for the 10% group differs significantly from the decrease for the sham group ($p = 0.02$). Likewise, the 4 groups differ with respect to the change in thickness of muscularis propria ($p = 0.03$). According to Scheffé the increase for the 10% group is significantly greater than the increase for the 4+2 cm group ($p = 0.04$). No significant differences among the groups have been found with respect to the changes in villous height and crypt height - villous height ratio.
If we also compare the jejunal wall parameters of each group at operation and after 16 weeks , some significant differences may be demonstrated by Student's paired tests.
In the sham group villous height has increased by 8% ($p > 0.10$), crypt height, however, has significantly decreased by 16% ($p = 0.008$). Consequently, the mean crypt-villus ratio has decreased from 0.42 to 0.33 ($p = 0.03$), indicating less generative epithelial activity. This 16% decrease in crypt height of sham rats is unexpected.
The thickness of muscularis propria has not increased significantly (11%).
In the 4+2 cm bypass group villous height of the jejunal part of the functional segment increases significantly by 11% ($p = 0.03$), and crypt height decreases not significantly by 5% ($p > 0.10$). In consequence the mean crypt-villus ratio

decreases significantly from 0.40 to 0.34 ($p = 0.005$).
Thickness of muscularis propria increases by 6% ($p > 0.10$).
Thus, except for villous height increase , unexpectedly little change in the functional jejunal wall is found after 4+2 cm bypass.
In the 10% bypass group villous height of the jejunal part of the functional segment increases significantly by 13% ($p = 0.004$), crypt height increases - non-significantly - by 4% and the crypt-villus ratio decreases from 0.38 to 0.35 ($p = 0.08$).
Thickness of muscularis propria increases significantly by 43% ($p < 0.001$).
Thus the functional jejunal segment is strongly affected by a 10% bypass.
In the p.c. shunt group neither of the microscopic parameters of the proximal jejunal wall changes significantly.
Since crypt height does not decrease, as it does in sham rats, the decrease in the sham group is probably not accounted for by diminished regenerative capacity, parallelling age.

6.5.3 Early changes in jejunal part of functional segment after a 4+2 cm jejunoileal bypass

In order to study early changes in the intestinal wall after 4+2 cm jejunoileal bypass we will compare the differences of intestinal wall parameters in three groups, sacrificed after 1, 2 and 16 weeks, respectively.
In each group data after operation are compared with values obtained at operation. The postoperative changes are calculated in table 6.4 (cf. biopsy 1a and 1b in fig. 6.3 and fig. 6.4).

rats sacrificed after	*N*	*Δ villus*	*Δ crypt*	*Δ musc.prop.*	*Δ entire wall*
1 week	*5*	*20 ± 92 (4%)*	*28 ± 39 (14%)*	*15 ± 19 (16%)*	*69 ± 108 (8%)*
2 weeks	*6*	*202 ± 111 (37%)**	*26 ± 47 (11%)*	*52 ± 47 (47%)*	*301 ± 158 (33%)**
16 weeks	*20*	*57 ± 110 (11%)**	*-11 ± 40 (-5%)*	*6 ± 25 (6%)*	*48 ± 139 (6%)*

*Table 6.4 Changes in microscopic parameters of functional jejunal wall occurring after jejunoileal bypass (mean and s.d. in μ and - between brackets - percentual mean change). * = significant (≤ 0.05) according to Student's paired test.*

All parameters of the functional jejunum increase after 1 week, though not significantly. After 2 weeks a greater and significant increase is found for all parameters except crypt height and afterwards the effect diminishes.
Since we do not know what happens between 2 and 16 weeks, we cannot conclude that hypertrophy reaches its maximum 2 weeks after operation.
The thickness of muscularis mucosae and tunica submucosa taken

together, which may be calculated as the thickness of the entire wall minus that of the sum of villus, crypt and muscularis propria, (cf. fig. 6.1), does not change much: an average increase of 6 mu, 21 mu and 4 mu after 1 week, 2 weeks and 16 weeks, respectively.
These differences in intestinal parameters at the various times after operation have been compared with a one-way analysis of variance together with a simultaneous multiple comparison method according to Scheffé. Then the overall hypothesis of equal changes in villous height has to be rejected ($p = 0.01$); the increase of villous height after 2 weeks is significantly greater than after 1 and 16 weeks ($p = 0.03$).
Change in crypt height tends to differ among the 3 periods ($p = 0.06$) but no significant difference is present between changes after 1 week and 2 or 16 weeks, or between changes after 2 weeks and 16 weeks.
Concerning the increase in thickness of muscularis propria the overall hypothesis of equal changes is rejected ($p = 0.009$). After 2 weeks the increase is significantly greater than that after 16 weeks ($p = 0.008$).
Likewise, the increase of the entire jejunal wall after 2 weeks is significantly greater than after 16 weeks ($p = 0.002$), but also greater than after 1 week ($p = 0.03$).
The crypt-villus ratio of the functional jejunum is 0.40 at operation, 0.44 after 1 week, 0.34 after 2 weeks and 0.34 after 16 weeks. The hypothesis of equal changes has to be rejected ($p = 0.04$). According to Scheffé this is possibly caused by the fact that the changes after 2 and 16 weeks differ from the change after 1 week ($0.05 < p < 0.07$).

6.5.4 Excluded proximal jejunum in 4+2 cm bypass group and 10% bypass group after 16 weeks compared with proximal jejunum at operation

The changes in microscopic parameters of the excluded proximal jejunum, observed 16 weeks postoperatively and compared with values measured at operation, are represented in table 6.5 for the 4+2 cm and the 10% jejunoileal bypass groups (cf. biopsy 3 and 1a in fig 6.3 and fig. 6.4).

	N	*Δ villus*	*Δ crypt*	*Δ musc.prop.*	*Δ entire wall*
4+2cm	*19*	*-14 ± 124(3%)*	*-24 ± 37(12%)**	*18 ± 28(19%)**	*-14 ± 122 (2%)*
10%	*23*	*20 ± 77(4%)*	*-18 ± 26(9%)**	*27 ± 33(31%)**	*32 ± 96 (4%)*

*Table 6.5 Changes in microscopic parameters of excluded proximal jejunum 16 weeks after a 4+2 cm or a 10% jejunoileal bypass (mean and s.d. in μ, and - between brackets - percentual mean change). * = significant; $p \leq 0.01$, Student's paired test.*

With the use of Student's paired tests the following conclusions may be drawn.
Villous height of the excluded jejunum in the 4+2 cm bypass group has diminished by 3% (not significantly) whereas the 10% bypass group shows an increase of 4% (not significant). The same holds good for the change in thickness of the entire wall (2% and 4%, respectively).
Crypt height of the excluded jejunum diminishes significantly in both groups by 12% (p = 0.01) and 9% (p = 0.003), respectively.
Thickness of muscularis propria increases significantly in both groups by 19% (p = 0.01)and 31% (p < 0.001) respectively. The fact that both villous height and thickness of entire wall do not change clearly, while the thickness of muscularis propria increases, is unexpected if we consider the clear macroscopic atrophy of the excluded jejunum. However, one should keep in mind that neither circumference of the intestine nor total mucosal surface have been taken into account.
Mean crypt-villus ratio in the 4+2 cm bypass group at operation is 0.40 and 0.36 after 16 weeks . This decrease is not significant.
In the 10% bypass group crypt-villus ratio is 0.38 at operation and 0.33 after 16 weeks . This decrease is significant (p = 0.003).

6.5.5 Early changes in excluded proximal jejunum after a 4+2 cm jejunoileal bypass

The microscopic parameters of excluded proximal jejunum, measured 1, 2 and 16 weeks postoperatively, have been compared with the data obtained at operation from the proximal jejunum (cf. biopsy 3 and 1a in fig. 6.3 and fig. 6.4). The postoperative changes are given in table 6.6 .

rats sacrificed after	*N*	*Δ villus*	*Δ crypt*	*Δ musc.prop.*	*Δ entire wall*
1 week	*5*	*-2 ± 108(0%)*	*6 ± 48(3%)*	*14 ± 25(14%)*	*28 ± 102 (3%)*
2 weeks	*6*	*12 ± 159(2%)*	*-32 ± 38(-14%)*	*17 ± 31(15%)*	*-10 ± 213 (-1%)*
16 weeks	*19*	*-14 ± 124(-3%)*	*-24 ± 37(-12%)**	*18 ± 28(19%)**	*-14 ± 122 (-2%)*

Table 6.6 Changes in microscopic parameters of the excluded proximal jejunum after 4+2 cm jejunoileal bypass (mean and s.d.in μ , and - between brackets - percentual mean change).
** = significant ($p \leq 0.01$) according to Student's paired test.*

According to separate Student's paired tests no significant changes after 1 week or 2 weeks are found ($p \geq 0.10$). Besides, with one-way analyses of variance for neither of the changes represented in table 6.6 significant differences among the 3

subgroups are found.
Also, thickness of muscularis mucosae and tunica submucosa do not change much (cf. 6.5.3).
Mean crypt-villus ratio is 0.40 at operation , 0.42 after 1 week , 0.37 after 2 weeks and 0.36 after 16 weeks .
Also these changes in crypt-villus ratio are not significantly different according to a one-way analysis of variance.

6.6 Ileum

6.6.1 Microscopic examination of ileum at operation

Biopsies of distal ileum were taken as described earlier (cf. 3.2.9, 3.3.3, 3.3.4 and 3.3.5) from all rats of the 4 experimental groups. This was also done with a group of fatty male Zucker rats with a 4+2 cm jejunoileal bypass sacrificed after 1 week or after 2 weeks (cf. biopsy 2a in fig. 6.3).
Thus we have 4 experimental groups with a subdivision of the 4+2 cm jejunoileal bypass group in as far as the period after operation is concerned : 1 week, 2 weeks and 16 weeks respectively.
Table 6.7 gives mean values of villous and crypt heights, thickness of muscularis propria and thickness of the entire wall in the ileum of male and female Zucker rats.

	N	*villus*	*crypt*	*musc.prop.*	*entire wall*
male	*29*	*355 ± 43*	*194 ± 25**	*100 ± 20*	*681 ± 62**
female	*34*	*337 ± 56*	*181 ± 20**	*93 ± 19*	*646 ± 74**

Table 6.7 Microscopic parameters of the distal ileum in male and female Zucker rats at operation (mean and s.d. in μ).
** = significant ($p \leq 0.05$) difference according to Student's test.*

In a Student's two sample test both crypt height and thickness of the entire wall of the distal ileum appear significantly greater in male rats than in female rats ($p = 0.02$ and $p = 0.05$, respectively).
Nevertheless, for two reasons we neglect the sex difference when comparing the 4 experimental groups (table 6.8). Both sexes are equally distributed over each of the groups. Secondly, both sexes appear to behave in the same way (increase, decrease or no change) when we examine the changes of the parameters of the intestinal wall.
One-way analyses of variance show that villous height, crypt height, thickness of muscularis propria and thickness of entire wall of the distal ileum do not differ significantly among the 4 groups.
Mean crypt-villus ratio of the ileum in these 63 rats is 0.55 at operation.

	N	villus	crypt	musc.prop	entire wall
sham	10	323 ± 47	195 ± 18	93 ± 23	648 ± 69
4+2cm	20	355 ± 48	186 ± 21	94 ± 19	666 ± 61
10%	23	338 ± 57	179 ± 25	95 ± 19	648 ± 81
p.c.s.	10	364 ± 40	201 ± 24	104 ± 22	702 ± 57

Table 6.8 Microscopic parameters of the distal ileum in 4 experimental groups at operation (mean and s.d. in μ).

<u>6.6.2 Distal ileum and ileal part of functional segment 16 weeks after operation</u>

Villous height, crypt height, thickness of muscularis propria and thickness of entire wall for the various experimental groups are given in table 6.9 . Biopsies were taken from the distal ileum in sham and p.c. shunt groups and from the jejunal part of the functional segment in 4+2 cm and 10% bypass groups (cf. biopsy 2a in fig. 6.3 and biopsy 2b in fig. 6.4).

	N	villus	crypt	musc.prop.	entire wall
sham	10	329 ± 68	180 ± 32	106 ± 33	662 ± 109
4+2cm	20	663 ± 100	209 ± 22	112 ± 26	1026 ± 122
10%	23	713 ± 162	219 ± 42	128 ± 28	1112 ± 228
p.c.s.	10	345 ± 56	176 ± 27	137 ± 62	700 ± 117

Table 6.9 Microscopic parameters of distal ileum in sham and p.c.s. groups and of ileal part of functional segment in 4+2 cm and 10% jejunoileal bypass groups 16 weeks after operation (mean and s.d. in μ).

For each group separately we have compared the data from tables 6.8 and 6.9 with the help of Student's paired tests. A minimal (2%), non-significant increase in thickness of the entire wall of the distal ileum is then found in the sham group.
Villous height, crypt height and thickness of muscularis propria also remain unchanged in the sham group.
Crypt-villus ratio of the distal ileum in the sham group at operation is 0.62 and it changes to 0.56 16 weeks after operation. This decrease is not significant.
In the 4+2 cm group all layers of the ileal part of the functioning segment have increased very significantly 16 weeks after operation : villous height by 87% (p = 0.0001), crypt height by 12% (p = 0.0008), thickness of muscularis propria by 19% (p = 0.005) and thickness of the entire wall of the ileal

part of the functional segment by 54% ($p = 0.0001$).
Mean crypt-villus ratio of the distal ileum in the 4+2 cm group at operation is 0.53 and it decreases significantly ($p = 0.0001$) to 0.32 16 weeks postoperatively.
In the 10% group all layers of the ileal part of the functional segment have increased even more, 16 weeks after operation: villus height by 111% ($p = 0.0001$), crypt height by 22% ($p = 0.0002$), thickness of muscularis propria by 35% ($p = 0.0002$) and thickness of the entire wall by 72% ($p = 0.0001$).
Here, crypt-villus ratio of the distal ileum is 0.54 at operation.Sixteen weeks postoperatively it has decreased significantly ($p = 0.0001$) to 0.32 .
In the portacaval shunt group the layers of the distal ileum do not show any consistent behaviour. Villous height diminishes by 5% ($p > 0.10$) crypt height diminishes by 12% ($p = 0.08$), while thickness of muscularis propria increases by 32% ($p > 0.10$) and thickness of the entire ileal wall remains nearly unchanged (0.3% decrease).
Crypt-villus ratio of the distal ileum in the p.c.s. group is 0.56 at operation and 0.53 16 weeks after operation; this decrease is not significant.
Next, the 4 groups have been compared with a one-way analysis of variance with respect to the changes after 16 weeks. The hypothesis of equal changes of villous height has to be rejected ($p < 0.001$). The 4+2 cm and 10% groups show a significantly greater increase of villous height in comparison with the change for the sham or p.c. shunt group ($p < 0.001$) according to the simultaneous comparison method of Scheffé.
There is no significant difference in increase of villous height between the 4+2 cm bypass group and the 10% group.
The changes in crypt height after 16 weeks are significantly different among the 4 groups ($p < 0.001$).
The 10% bypass group shows a significantly greater increase in crypt height in comparison with the change in the sham group and the p.c.s. group ($p = 0.004$ and $p < 0.001$, respectively), whereas the change in crypt height of the 4+2 cm bypass group differs nearly significantly ($p = 0.09$) from that measured in the sham group and significantly ($p = 0.02$) from that in the p.c.s. group.
After 16 weeks changes in the thickness of the muscularis propria in the 4 groups are not found to be significantly different.
The hypothesis of equal changes for the thickness of the entire wall also has to be rejected ($p < 0.001$). The increase of the thickness of the entire wall of the distal ileum in the 4+2 cm and 10% bypass groups is significantly different from the change in the sham group or the p.c.s. group ($p < 0.001$).
The changes in thickness of the entire wall of the distal ileum observed after either 4+2 cm or 10% jejunoileal bypass do not differ significantly.

6.6.3 Early changes in ileal part of functional segment after a 4+2 cm jejunoileal bypass

The changes in the ileal part of the functional segment of a 4+2 cm jejunoileal bypass observed 1 week, 2 weeks and 16 weeks postoperatively are presented in table 6.10 (cf. biopsy

2a in fig. 6.3 and biopsy 2b in fig. 6.4).
Data obtained after operation are compared with values measured at operation and the calculated postoperative changes are given.

rats sacrificed after	*N*	*Δ villus*	*Δ crypt*	*Δ musc.prop*	*Δ entire wall*
1 week	*5*	*312 ± 147 (112%)**	*50 ± 53 (28%)*	*34 ± 36 (42%)*	*397 ± 114 (69%)**
2 weeks	*6*	*405 ± 107 (135%)**	*47 ± 24 (25%)**	*54 ± 42 (64%)*	*494 ± 119 (79%)**
16 weeks	*20*	*308 ± 100 (87%)**	*23 ± 26 (12%)**	*17 ± 25 (19%)*	*360 ± 122 (54%)**

*Table 6.10 Changes in microscopic parameters of functional ileal part of a 4+2 cm jejunoileal bypass (mean and s.d. in μ , and - between brackets - percentual mean change). * = significant ($p < 0.05$) according to Student's paired test.*

A considerable increase in all parameters of the functional ileum is visible ,particularly 2 weeks after operation.
Again, as in the jejunal part of the functional segment (6.5.3) muscularis mucosae and tunica submucosa do not change much with a mean increase of 1 mu, a decrease of 12 mu and an increase of 12 mu after 1 week, 2 weeks and 16 weeks respectively.
After 1 week the increases of villous height and thickness of the entire wall are significant ($p < 0.01$) according to Student's paired tests.
After 2 weeks the increase, expressed as percentages of values at operation, amounts to 135% for villous height, 25% for crypt height, 64% for thickness of muscularis propria and 79% for thickness of the entire functional ileal wall.All increases are significant ($p \leq 0.02$).
If we compare the differences in intestinal parameters , measured at the various times after operation with a one-way analysis of variance neither the increase of villous height nor the increase of crypt height is significantly different after 1, 2 and 16 weeks.
The hypothesis of equal increases for the thickness of muscularis propria has to be rejected ($p = 0.04$). According to the method of Scheffé the increase in thickness of muscularis propria is greater after 2 weeks than after 16 weeks ($p = 0.05$).
Possibly the increases in thickness of the entire wall in the functional ileal part are also different for the 3 times ($p = 0.07$). The increase tends to be greater after 2 weeks than after 16 weeks ($p = 0.07$) according to Scheffé.
Mean crypt-villus ratio of the functional ileum is 0.53 at operation (if only based on the 16-week rats; the mean value at operation of all 1-week, 2-week and 16-week rats amounts to 0.57), 0.43 after 1 week, 0.34 after 2 weeks and 0.32 after 16 weeks.

These changes in crypt-villus ratio are significant after 2 weeks and 16 weeks (Student's paired test: $p < 0.001$). However, no different changes are found according to a one-way analysis of variance ($p > 0.10$).

6.6.4 Excluded distal ileum in 4+2 cm bypass group and 10% bypass group after 16 weeks in comparison with distal ileum at operation

The microscopic parameters, observed in the excluded distal ileum 16 weeks after a 4+2 cm or a 10% jejunoileal bypass, have been compared with those measured in the distal ileum at operation (cf. biopsy 4 and 2a in fig. 6.4 and fig. 6.3). The calculated changes are expressed in table 6.11 .

	N	Δ villus	Δ crypt	Δ musc.prop.	Δ entire wall
4+2cm	20	1 ± 83 (0.3%)	-7 ± 37 (-4%)	34 ± 46 (36%)*	43 ± 139 (6%)
10%	23	101 ± 111 (30%)*	7 ± 40 (4%)	28 ± 46 (29%)*	150 ± 173 (23%)*

*Table 6.11 Changes in microscopic parameters of excluded distal ileum 16 weeks after a 4+2 cm or a 10% jejunoileal bypass (mean and s.d. in μ , and - between brackets - percentual mean change). * = significant, $p < 0.01$, Student's paired test.*

With separate Student's paired tests the following results are obtained.
Villous height of the excluded ileum in the 4+2 cm bypass group does not change whereas it shows a significant increase of 30% ($p = 0.0002$) in the 10% group.
Crypt height diminishes slightly (4%) and increases slightly (4%) in the 4+2 cm bypass group and the 10% bypass group , respectively (both changes are not significant).
Thickness of muscularis propria increases significantly in both groups by 36% ($p = 0.003$) and 29% ($p = 0.007$), respectively.
Mean thickness of the entire wall increases by 6% ($p > 0.10$) in the 4+2 cm bypass group and by 23% ($p = 0.0004$) in the 10% group .
Crypt-villus ratio in the 4+2 cm bypass group is 0.53 at operation and after 16 weeks 0.52 in the excluded distal ileum. This decrease is not significant.
In the 10% bypass group mean crypt-villus ratio at operation is 0.54. Sixteen weeks after operation this has significantly ($p = 0.007$) decreased to 0.45 in the excluded ileum.

6.6.5 Early changes in the excluded distal ileum after a 4+2 cm jejunoileal bypass

The microscopic parameters of excluded distal ileum, measured 1, 2 and 16 weeks after operation, have been compared with the data obtained at operation from the distal ileum (cf. biopsy 4 in fig. 6.4 and biopsy 2a in fig. 6.3). The postoperative changes are given in table 6.12 .

rats sacrificed after	N	Δ villus	Δ crypt	Δ musc.prop.	Δ entire wall
1 week	5	112 ± 96 (20%)	10 ± 39 (6%)	29 ± 36 (37%)	151 ± 154 (26%)
2 weeks	6	184 ± 144 (61%)*	31 ± 34 (16%)	58 ± 27 (68%)*	255 ± 170 (41%)*
16 weeks	20	1 ± 83 (0.3%)	-7 ± 37 (-4%)	34 ± 46 (36%)*	43 ± 139 (6%)

*Table 6.12 Changes in microscopic parameters of excluded distal ileum after 4+2 cm jejunoileal bypass (mean and s.d. in μ , and - between brackets - percentual mean change). * = significant ($p < 0.05$) according to Student's paired test.*

According to separate Student's paired tests villous height has increased nearly significantly ($p = 0.06$) by 20% after 1 week and significantly ($p = 0.03$) by 61% after 2 weeks. After 16 weeks it has decreased again to the value measured at operation. The hypothesis that the changes for the 3 periods are equal, has to be rejected ($p = 0.001$, one-way analysis of variance).
A further analysis according to Scheffé does not clearly show that the change in villous height, measured after 1 week differs from the change measured 16 weeks postoperatively ($p = 0.10$).
If the change, measured after 2 weeks, is compared to the change measured after 16 weeks, a significantly ($p = 0.002$) diminished effect is present in the latter group.
Crypt height of the excluded ileum has increased by 6% after 1 week and by 16% after 2 weeks, while after 16 weeks it has diminished by 4%. None of these changes is statistically significant. The changes in crypt height measured after 1 week, 2 weeks and 16 weeks do not differ significantly (one-way analysis of variance).
Thickness of muscularis propria of the excluded distal ileum increases by 37% ($p > 0.10$) after 1 week, and by 68% after 2 weeks ($p = 0.003$) and still shows a significant increase of 36% after 16 weeks ($p = 0.003$). No significant differences among the 3 changes are found ($p > 0.10$; analysis of variance).
Thickness of the entire wall of the excluded distal ileum increases by 26% (n.s.) after 1 week and by 41% after 2 weeks ($p = 0.01$). After 16 weeks a small non-significant increase (6%) is still present.

According to an anlysis of variance the hypothesis of equal mean changes after 1, 2 and 16 weeks, has to be rejected ($p = 0.01$). The method of Scheffé shows that the increase in thickness of the entire wall of the excluded distal ileum for rats killed after 2 weeks differs from the increase in rats sacrificed after 16 weeks ($p = 0.02$).
There is not much room for changes in thickness of muscularis mucosa and tunica submucosa (cf. 6.5.3 and 6.5.5).
Mean crypt-villus ratio of the distal ileum at operation is 0.57, 0.49 after 1 week, 0.48 after 2 weeks and 0.52 after 16 weeks. The changes after 1 week and 2 weeks are significant ($p = 0.03$ and $p = 0.01$ respectively). The hypothesis of equal changes for the 3 periods has to be rejected ($p = 0.03$; analysis of variance), but an analysis according to Scheffé does not demonstrate any differences between 2 periods ($p > 0.10$).

6.7 Comparison of microscopic parameters of jejunum and ileum in fat and lean Zucker rats

Mean values of villous height, crypt height, thickness of muscularis propria and thickness of the entire wall of jejunum and ileum in 121 male and female fatty Zucker rats and 4 male lean Zucker rats are given in table 6.13.
The mean age of fatty rats is 121 days and the mean age of lean rats is 131 days.

rat	*N*	*villus*	*crypt*	*musc.prop.*	*entire wall*
	jejunum				
fatty	*121*	*525 ± 60**	*204 ± 28*	*93 ± 20*	*859 ± 75**
lean	*4*	*448 ± 57**	*196 ± 16*	*82 ± 14*	*748 ± 72**
	ileum				
fatty	*121*	*336 ± 55**	*186 ± 26*	*95 ± 23*	*654 ± 82*
lean	*4*	*269 ± 56**	*182 ± 41*	*97 ± 19*	*579 ± 115*

Table 6.13 Microscopic parameters of jejunum and ileum in fatty and lean Zucker rats at operation (mean and s.d. in μ).
** = significant difference between fatty and lean rats, $p < 0.02$, Student's test.*

The values of intestinal parameters in fatty and lean Zucker rats at operation have been compared with the help of a Student's two sample test. In fatty rats, both villous height and thickness of the entire wall of jejunum are significantly greater than in lean rats, 17% ($p = 0.02$) and 15% ($p = 0.004$) respectively, whereas no significant difference exists in crypt height or thickness of muscularis propria .
Ileal villous height is 25% greater in fatty rats than in

lean rats (p = 0.01) and thickness of the entire ileal wall tends to be greater in fatty rats (13%, p = 0.07).
Crypt height and thickness of muscularis propria in the ileum are not significantly different for fatty and lean Zucker rats.
Mean crypt-villus ratio of the jejunum in fatty rats is 0,39 and 0.44 in lean rats . The difference is not significant.
Mean crypt-villus ratio of the ileum in fatty rats is 0.57 and 0.68 in lean rats , which is significantly higher (p = 0.03).

6.8 Hypertrophy of the functional intestine , atrophy of the excluded segment and reflux into the excluded distal ileum 16 weeks after a 4+2 cm or a 10% jejunoileal bypass

6.8.1 Macroscopic hypertrophy and microscopic measurements of the functional segment 16 weeks after a 4+2 cm and 10% jejunoileal bypass

Macroscopic hypertrophy of the functional segment in the 4+2 cm bypass group and the 10% bypass group after 16 weeks is equally frequent in both groups (see 6.4.1 for definition and number of rats). Therefore, both groups can be studied together.
Since elongation and dilatation of the functional intestine after bypass are not necessarily correlated with hypertrophy of the layers of the intestinal wall, a possible relation has been investigated.
Table 6.14 gives the changes in microscopic parameters of jejunum and ileum of the functional segment, 16 weeks after bypass, both in rats with little and in rats with much macroscopic hypertrophy.

hypertrophy	*N*	*Δ villus*	*Δ crypt*	*Δ musc. prop.*	*Δ ent. wall*
jejunum					
little	*3*	*123 ± 121*	*13 ± 94*	*47 ± 80*	*167 ± 308*
much	*40*	*59 ± 104*	*-2 ± 33*	*21 ± 32*	*78 ± 121*
ileum					
little	*3*	*505 ± 109**	*38 ± 54*	*38 ± 41*	*597 ± 195*
much	*40*	*331 ± 141**	*32 ± 37*	*25 ± 31*	*402 ± 191*

Table 6.14 Changes in microscopic parameters of functional jejunum and ileum 16 weeks after 4+2 cm or 10% jejunoileal bypass in rats with little and in rats with much macroscopic hypertrophy of the functional segment (mean and s.d. in μ).
** = significant difference (p = 0.04) between little and much hypertrophy according to Student's two-sample test.*

Table 6.14 shows that when little elongation and dilatation of the functional segment occurs the increase of all parameters

of the jejunal and ileal wall is greater than in a situation where much hypertrophy is present.
These differences , however, are not significant with the exception of the difference for the villous height in the ileum ($p = 0.04$). This is probably due to the large variation and the small number of rats showing little hypertrophy.
These results indicate that elongation and dilatatation of the intestinal wall and increase in thickness of the layers of the intestinal wall are probably the result of separate mechanisms of adaptation.

6.8.2 Macroscopic atrophy and microscopic measurements of the excluded segment 16 weeks after 4+2 cm or 10% jejunoileal bypass

Macroscopic atrophy of the excluded segment is defined as a clearly visible reduction in diameter and length (cf. 6.4.1). This reduction is visible in fig. 6.5 .
The excluded segment is almost entirely coiled into one knot and of a yellow pink appearance due to inspissated mucous.
Rats with much and rats with little macroscopic atrophy of the excluded segment are distributed in the same way in the 4+2 cm bypass group as in the 10% bypass group.
Hence both groups will be considered together.
Table 6.15 gives the changes in microscopic parameters of jejunum and ileum of the excluded segment, 16 weeks after bypass, both in rats with little and in rats with much macroscopic atrophy.

atrophy	*N*	*Δ villus*	*Δ crypt*	*Δ musc.prop.*	*Δ ent. wall*
	jejunum				
little	*7*	*4 ± 114*	*-23 ± 30*	*41 ± 28*	*21 ± 140*
much	*35*	*4 ± 101*	*-20 ± 32*	*19 ± 30*	*9 ± 105*
	ileum				
little	*7*	*61 ± 119*	*7 ± 42*	*47 ± 53*	*127 ± 201*
much	*35*	*53 ± 110*	*-1 ± 39*	*28 ± 44*	*95 ± 160*

Table 6.15 Changes in microscopic parameters of the excluded jejunum and ileum 16 weeks after 4+2 cm or 10% jejunoileal bypass in rats with little and in rats with much macroscopic atrophy of the excluded segment (mean and s.d. in μ).

Table 6.15 shows that, generally, if little reduction in diameter and length of the excluded segment is found the increase of nearly all parameters of the jejunal and ileal wall is slightly greater than in a situation where much atrophy is present.

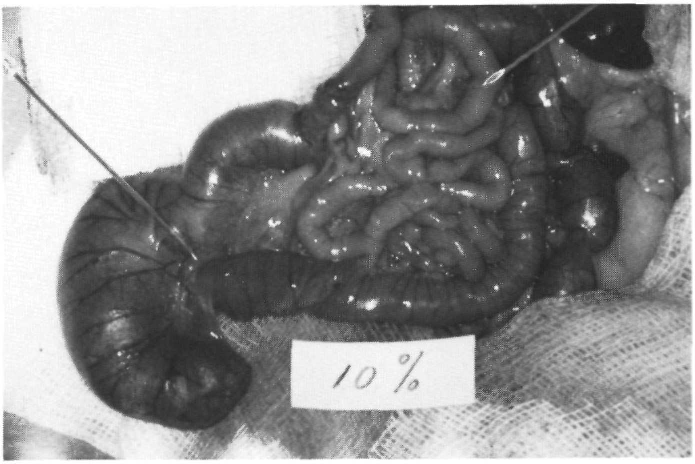

Fig. 6.5. *Autopsy specimen 16 weeks after 10% jejunoileal bypass in the fat Zucker rat. Clear hypertrophy of the functional intestinal segment (between both needles in lower part of picture).*
Clear atrophy of the excluded intestine (middle of the picture. Cecomegaly (left).

Fig. 6.6. *Female fat Zucker rat. Age 12 weeks, weight: 305 g (left). Female fat Zucker rat, 5 weeks after 4+2 cm jejunoileal bypass.Weight: 203 g.*
Age at operation 13 weeks and weight: 301 g (right).

However, in a Student's -two sample test no statistically significant difference in change of jejunal and ileal wall parameters can be shown between rats with little or rats with much atrophy of the excluded segment.

6.8.3 Macroscopic reflux into the excluded segment and microscopic measurement of the excluded segment 16 weeks after 4+2 cm and 10% jejunoileal bypass

Since reflux with chyme into the distal excluded small intestine and thus undesired resorption of nutrients by the excluded segment, has been mentioned as a possible cause for insufficient weight reduction after jejunoileal bypass (Payne, 1980), this phenomenon was studied and compared with microscopic ileal wall parameters 16 weeks after construction of the bypass.
In the 4+2 cm bypass group 8 rats show reflux into the distal excluded ileum and 12 show no reflux whereas in the 10% bypass group 11 rats show reflux and 12 show no reflux. This difference in frequency is not significant (chi-square test).
Thus all rats with a bypass may be considered as one group.
Table 6.16 gives the changes in microscopic parameters of the excluded proximal jejunum and distal ileum, 16 weeks after a 4+2 cm or a 10% jejunoileal bypass, both in rats where reflux is present and in rats where reflux is absent.

reflux	*N*	Δ *villus*	Δ *crypt*	Δ *musc.prop.*	Δ *ent.wall*
prox.jejunum					
absent	*24*	-19 ± 115	-21 ± 24	18 ± 26	-17 ± 110
present	*18*	35 ± 71	-21 ± 40	29 ± 36	48 ± 101
dist.ileum					
absent	*24*	47 ± 112	4 ± 31	51 ± 36*	121 ± 154
present	*18*	64 ± 109	-4 ± 48	6 ± 44*	74 ± 180

Table 6.16 Changes in microscopic parameters of excluded proximal jejunal and distal ileal wall 16 weeks after jejunoileal bypass in rats with and without reflux into the excluded segment (mean and s.d. in μ).
** = significant difference ($p < 0.001$) between presence of reflux and absence of reflux according to Student's test.*

Villous height of the excluded proximal jejunum seems to decrease when reflux into the excluded distal ileum is absent, whereas villous height seems to increase when reflux into the excluded distal ileum takes place. However, the difference between those changes is not clearly significant ($p = 0.08$) according to a Student's two-sample test.
In the distal ileum villous height increases whether reflux is

present or not. If reflux occurs the increase in villous height seems to be more enhanced (not significant).
Crypt height in the excluded proximal jejunum seems to decrease irrespective of presence of reflux whereas in the distal ileum no change of crypt height is observed.
Thickness of muscularis propria increases slightly more in the excluded proximal jejunum when reflux into the distal ileum occurs (not significant). In the distal ileum the situation is exactly the reverse: an increase of thickness of muscularis propria of the ileum is observed if reflux is absent and no change if reflux is present. This difference in increase is significant ($p = 0.001$).
Thickness of the entire wall of the excluded proximal jejunum seems to diminish if reflux into the distal ileum is absent but seems to increase if present. The difference is almost significant ($p = 0.06$).
In the distal ileum the situation is almost the reverse: there is a clear increase of thickness of the entire wall if reflux is absent and a smaller increase if reflux is present. The difference is not significant.
When comparing the change of thickness of the entire wall of the excluded proximal jejunum with the value of jejunum of sham rats 16 weeks after operation (see table 6.3), we notice that the decrease comes to 2% if reflux is absent whereas the increase comes to 5% if reflux is present.
When comparing the change of thickness of the excluded distal ileal wall with the value of ileum of sham rats 16 weeks after operation (see table 6.9), the increase comes to 18% if reflux is absent and to 11% if reflux into the distal ileum is present. Thus, no clear relation exists between the macroscopic aspect of reflux into the distal ileum and the microscopic parameters of the excluded proximal jejunum and the excluded distal ileum.

6.9 Discussion

Intestinal adaptation after large resection of small intestine in man has been known for many years (Dowling, 1966).
This adaptation has been studied in animals, especially in rats and to a lesser extent in dogs (Bochkov, 1958, 1959; Hanson, 1977, a and b).
Adaptation appears to be the same after resection or bypass and shows itself in elongation and dilatation of the remaining functioning intestine.
Apart from these macroscopic changes microscopic changes occur, such as increase of villous height, number of villi and thickness of the muscular coat.
In most cases, as in our study, the term hypertrophy is used although from a histological point of view, the term hyperplasia would be more accurate since the total number of normal-sized cells increases (Nygaard, 1967).
The intestinal mucosa is a dynamic three-dimensional structure. Enteric epithelium is completely replaced in mice and rats within 2 to 3 days and in man within 3 to 6 days (Williamson, 1978).
Criticism of morphometric methods is to a certain extent justified, because they yield a static two-dimensional

picture.
If, however, they are applied in a comparative study, measurements are certainly of great use.
Morphometric studies in man, previously subjected to jejunoileal bypass for morbid obesity and requiring relaparotomy for various reasons or having peroral biopsies after some time, show increased villous height in both jejunum and ileum which remained in continuity.
The increase of villous height in jejunum ranges between 38% and 88%. Most authors agree that villous height in the ileal part shows a greater increase.(Grenier,1974; Solhaug, 1976; Iversen, 1976; Fenyö, 1976; Grenier, 1977; Barry, 1977; Dudrick, 1977; Daly, 1977; Friedman, 1978, 1981; Fairclough, 1980).
Increase of crypt height seems to be confined to the ileal part of the functional intestine. Elongation and dilatation always occurs.
The bypassed segment usually becomes narrower, whereas shortening is not reported. Reports about changes in villous height in the excluded segment vary greatly. However, an increase has only been reported in the distal ileum. Other layers of the wall of the excluded segment have not been investigated.
Some more morphometric studies have been performed in rats (Tilson,1972, Nygaard, 1967).
The results are similar to those obtained in man. Again many authors confine their investigation to the mucosal part of the intestine.
No morphometric study has so far been published about the effects of jejunoileal bypass in fat Zucker rats.
The degree of adaptation in fat Zucker rats is interesting since preoperative microscopic parameters of the small intestine are already different from those obtained from lean rats. Mean villous height in jejunum (525 mu) and ileum (336 mu) of fat Zucker rats is significantly greater than in lean Zucker rats (448 mu and 269 mu respectively, see table 6.13), whereas in the commonly used Wistar or Sprague-Dawley rat villous height of the jejunum is even less, viz. 419 mu (Menge, 1974) or 364 mu (Marescaux, 1981).
When we consider adaptation of the functioning jejunum and ileum after jejunoileal bypass in our study, we find no change in length after 1 week, a shortening of 9% after 2 weeks and an elongation of 16% after 16 weeks.
After 16 weeks the ileal part of the functioning segment has increased slightly more than the jejunal part.
Sachdev (1979) reports different results in Sprague-Dawley rats of the same age. After a 5% + 5% end-to-side jejunoileal bypass a 22% increase of the length of the functioning intestine was found after 1 week, a 42% increase after 4 weeks and a 80% increase after 1 year.
The jejunal segment increased slightly more than the ileal segment (55% versus 45%).
This discrepancy might be explained by the difference of total small intestinal length, which is greater in Zucker rats . The intestine of these rats exists possibly already in a more or less adapted state, induced by increased oral intake.
The mean shortening of length of the functional segment, by 9%

two weeks after operation, is in apparent contrast to the observed increase (33%) of thickness of the layers of the functioning jejunum (cf. table 4.8 and table 6.4).
This might suggest two separate, successive mechanisms of adaptation: firstly the increase of thickness of the intestinal wall, mostly by increase of villous height and muscularis propria and secondly the increase in length and circumference.
After reaching a probable maximum of length and circumference, the thickness of the intestinal wall diminishes again, though it remains of a higher degree than before the operation, suggesting an equilibrium with a maximal absorptive surface.
This might explain why the ileum still shows such tremendous increase of thickness of intestinal wall, especially of villous height, 16 weeks after 4+2 cm or 10% jejunoileal bypass, when it has reached its maximal elongation and circumference (cf.tables 6.8, 6.9 and 4.8).
The functioning jejunum shows less elongation and less increase of villous length, starting from a more advantageous position preoperatively, viz. twice the length of the functioning ileum, with a larger circumference, taller villi and in the possession of Kerckring's folds.
Only two authors (Nygaard, 1967 c,d, and Nemeth, 1981) have published about the adaptation of intestinal muscle in the in-continuity segment after jejunoileal bypass.
Nygaard describes hypertrophy of the muscular layers of the small bowel after 75% resection or bypass and an increase of gastrointestinal transit-time 7 days after resection of 75% of the small intestine. Fourteen days after operation gastro-intestinal transit-time had decreased again.
Nemeth (1981) shows enhanced rapid transit-time 3 days after 70% end-to-end jejunoileal bypass in rats, but after 35 days the transit-time is again at the level of the control animals. Both wet weight and protein content of muscle were increased 35 days after operation, supporting the hypothesis that the adaptation in the in-continuity segment after jejunoileal bypass involves changes in function and structure of the intestinal smooth muscle as well as of the intestinal mucosa.
The stimuli which eventually result in increased muscle weight and protein content are not known. Possibly the bulk of intestinal contents, which is postulated to stimulate mucosal adaptation, also activates muscular adaptation.
In our experiment we have measured an increase of muscularis propria in the functioning jejunum of the 4+2 cm bypass group and 10% bypass group which is not significant, however, in comparison with the sham group (cf.tables 6.2 and 6.3).
The same holds good for the functioning ileum (cf. tables 6.8 and 6.9).
However, in the 10% bypass group a significant 43% increase is present after 16 weeks if the postoperative thickness of muscularis propria is measured against the value at operation.
After a 4+2 cm jejunoileal bypass, there is an increase of muscularis propria of the functioning jejunum of 16%, 47% and 6%, as measured 1, 2 and 16 weeks after operation respectively. For the functioning ileum these values are 42%, 64% and 19%, respectively. Thus, after a maximum increase measured 2

weeks postoperatively, a small increase could still be observed 16 weeks after operation.
The crypt-villus ratio, measure of enterocyte lifespan, in the functioning jejunum has increased from 0.40 to 0.44 1 week after a 4+2 cm jejunoileal bypass. Subsequently, after both 2 and 16 weeks, a value of 0.34 is found.
Thus enterocytes show a maximal functional period 1 week after operation.
In the functioning ileum life span seems to diminish steadily: a ratio of 0.53 at operation, 0.43 after 1 week, 0.34 after 2 weeks and 0.32 after 16 weeks, about the same as found in the functioning jejunum 16 weeks after operation.
According to the classification of abnormal villous patterns as given by Lee (1980), the functioning jejunum and ileum show the hypertrophic pattern as observed during lactation and after elemental nutrition in experimental animals (Elias and Dowling, 1976, Nelson, 1978). He considers it a true enterocyte hyperplasia in response to functional demand.
At present no explanation can be given for the considerable increase of muscularis propria, found 16 weeks after the construction of a portacaval shunt, both in jejunum (21%) and in ileum (32%), although these changes were not clearly significant. One would expect no change of the small intestine at all unless a humoral factor, produced by the liver and affecting adaptation, were to exist.
Changes in the layers of the functioning intestine are limited to villous height and muscularis propria and to a smaller extent, to crypt height, whereas muscularis mucosae and submucosa do not play any significant part.
For the excluded segment reports are contradictory.
Sachdev (1979) found after a 10% end-to-side bypass in rats a decrease of intestinal length of the bypassed segment of approximately 10%, measured after 1 week,4 weeks and 1 year.
The circumference of the proximal part of the bypassed segment (jejunum) had not changed after 1 week.
After 4 weeks, however, and after 1 year, a 35% decrease of circumference was observed. In contrast, a 50% increase of circumference of the distal end (ileum) was found after 1 week and a 70% and 74% increase after 4 weeks and 1 year, respectively.
In our experiment atrophy of the excluded segment becomes visible between 1 and 2 weeks after operation and is always present after 16 weeks.
In contrast, the layers of the excluded jejunum show little change after 1, 2 or 16 weeks. A small decrease of crypt height and a minimal increase of muscularis mucosae are observed. The increase of muscularis mucosae might be explained by more or less futile efforts of the excluded bowel to propel the enclosed inspissated mucus .
This hypothetical phenomenon may account for the abdominal cramps, which are observed very frequently in patients after jejunoileal bypass, and may correlate with the syndrome which is called bypass enteritis .
Villous height , muscularis mucosae, tunica submucosa and total thickness of the excluded proximal jejunum do not change after jejunoileal bypass. This again indicates the existence

of two separate adaptation mechanisms : decrease of length and circumference of the intestine and hardly any change of villous height and the other intestinal layers of the excluded segment.
The excluded distal ileum behaves in a way different from the excluded proximal jejunum.
One week after jejunoileal bypass the entire wall has increased in thickness by 26% and after two weeks this increase is 41%. Especially villous height and thickness of muscularis propria increase (by 61% and 68%, respectively after 2 weeks, cf. table 6.12).
After 16 weeks the thickness of the entire wall of the excluded ileum has decreased again,but it still remains 6% greater than the value at operation.
Villous height has then been reduced to the value at operation whereas crypt height has diminished slightly (by 4%).
It is worth noticing that, as with the excluded jejunum,the thickness of the muscularis propria has maximally increased by 68% 2 weeks after operation and that still a considerable increase of 36%, compared with the value at operation, remains 16 weeks postoperatively.
This remarkable increase may again be explained by efforts to propel inspissated mucus in the ascending colon.
Neither muscularis mucosae nor tunica submucosa change in thickness.
If little macroscopic atrophy of the excluded intestine is present one expects a different thickness of the intestinal layers as compared to the situation where much atrophy of the excluded intestine exists. This does not clearly prove to be the case.
If reflux of chyme from the ascending colon into the excluded distal ileum is present one expects a change in thickness of the intestinal layers, in comparison with a situation where such reflux is absent.
This only proves to be the case for the muscularis propria and indicates once more the existence of two separate adaptation mechanisms in the small intestine.
Mean crypt-villus ratio in the jejunum of fatty rats in the 4+2 cm group at operation is 0.40. It diminishes to 0.33 in the excluded jejunum 16 weeks after construction of a 4+2 cm jejunoileal bypass. Decrease of crypt height (12%) contributes relatively more to the lowering of this ratio than the decrease of villous height (3%). This may indicate, apart from a decline in generative epithelial activity, a slightly diminished enterocyte population.
In the classification of abnormal villous patterns, the excluded jejunum shows a hypoplastic pattern. This pattern has been observed in experimental radiation enteritis, intestinal ischaemia, following cytotoxic drugs and in patients who are either chronically ill or obviously undernourished (Lee,1980). In the last case this pattern is probably a morphological expression of reduced functional demand,a situation similar to that of the excluded jejunum .
The crypt-villus ratio of the distal excluded ileum shows less change than in the excluded jejunum. It changes from 0.53 at operatiom to 0.50 16 weeks later in the 4+2 cm bypass group.

In this group villous height has not changed after 16 weeks whereas crypt height has diminished by 4%, pointing to a slightly lessened generative epithelial activity.
Reflux of chyme may play some part here.
If we compare the intestinal adaptation , as expressed by microscopic measurements, 16 weeks after a 4+2 cm jejunoileal bypass, which is actually a bypass of 7% of the small intestinal length, and 16 weeks after a 10% jejunoileal bypass we find in all parts of the intestine - the functioning jejunum, the functioning ileum, the excluded jejunum and the excluded ileum - that the 4+2 cm bypass induces less hypertrophy in the functioning parts and more atrophy in the excluded parts than the 10% bypass .
One would expect just the opposite, viz. more adaptation, particularly in the functioning part, because it is shorter after a 4+2 cm bypass than after a 10% bypass. The fact that this does not happen, suggests that somewhere between a 7% and a 10% bypass a maximal adaptation occurs. Shortening the bypass below this point does not result in further adaptation, but, on the contrary, in decompensation, probably on account of too much malnutrition.
This phenomenon is also reflected in the weight curves after the 4+2 cm and 10% jejunoileal bypasses (cf. fig. 4.1).
Many experiments have been performed investigating the regulating mechanisms which result in hypertrophy and atrophy of the small intestine.
Williamson (1978 a and b) gives an extended review on intestinal adaptation.
Intestinal growth appears to be controlled by a feed-back mechanism which is regulated by a number of extrinsic agents. Food and enteric secretions, particularly bile and pancreatic juice, play a dominant part but cannot account for all aspects of the compensatory response. Systemic factors, implicated by adaptive changes in sequestered bowel, must also contribute to intestinal hyperplasia, both after partial tissue loss and in other conditions, including diabetes, hyperthyroidism and hypothermia.
Enterotropic hormones might be either stimulatory or inhibitory in nature. In addition the nerves, arteries and bacterial flora of the bowel may influence epithelial cell proliferation. Since the secretory and hormonal outputs of the gut are related to the presence or absence of nutrients in the small bowel lumen, the regulation of intestinal adaptation must involve several interdependent factors.

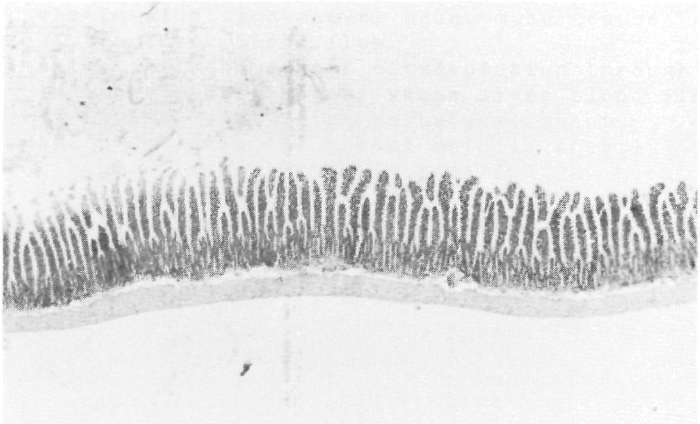

Fig. 6.7. Jejunum of the fat Zucker rat at operation. (H.E. : x 26).

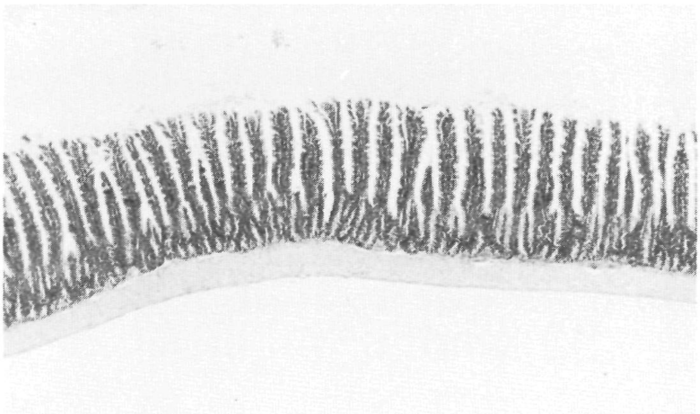

Fig. 6.8. Jejunal part of functional shunt at autopsy 16 weeks after 4+2 cm jejunoileal bypass. Clear hypertrophy of villi. (H.E. : x 26).

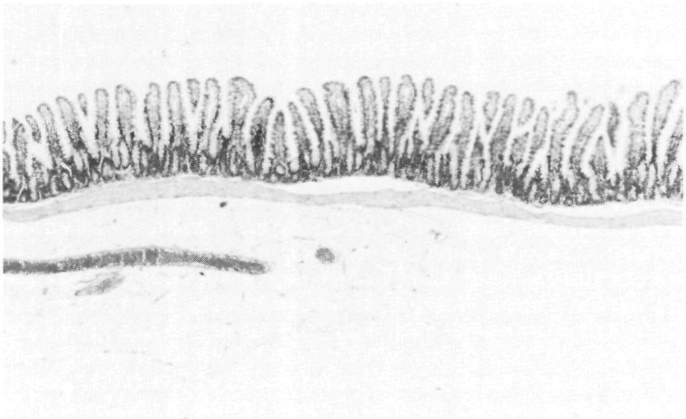

Fig. 6.9. Ileum of the fat Zucker rat at operation. (H.E. : x 26).

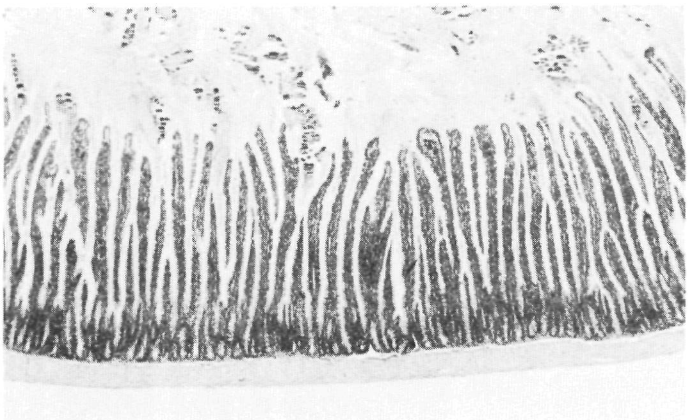

Fig. 6.10. Ileal part of functional shunt at autopsy 16 weeks after 4+2 cm jejunoileal bypass. Clear hypertrophy of villi. (H.E. : x 26).

6.10 Summary

Intestinal adaptation occurs after extensive resections and bypass procedures of the small intestine.
Adaptation of the small intestine appears to consist of two separate and subsequent mechanisms : firstly, an increase of thickness of the entire intestinal wall, mostly by increase of villous height and muscularis propria, and secondly an increase of intestinal length and circumference, including the number of villi and crypts.
Both mechanisms enlarge the absorptive mucosal surface.
In the fat Zucker rat adaptation of the intestine after jejunoileal bypass has not been demonstrated before.
In the fat Zucker rat the intestine is longer and the thickness of both jejunum and ileum is greater than in lean Zucker rats. This is mainly due to an increase of villous height.
As a result of overeating the fat Zucker rat already finds itself in an adapted state compared with the lean Zucker rat.
Sixteen weeks after a 4+2 cm jejunoileal bypass in fat Zucker rats the length of the functioning segment has increased by 16%. The functioning ileal part increases more than the jejunal part (20% versus 14%).
After 16 weeks the thickness of all layers together of the functioning jejunum has increased by 6% and of the functioning ileum by 54%.
A 10% jejunoileal bypass in these Zucker rats shows even more adaptation after 16 weeks: an increase of 14% for the thickness of the jejunal part of the functioning segment and an increase of 72% in the ileal part.
Of all the layers of the intestine villous height shows the greatest adaptive response, followed by the muscularis propria and to a smaller extent crypt height.
Changes in muscularis mucosae and tunica submucosa are not important.
Thus the mucous membrane plays a dominant part in intestinal adaptation.
The length of the functioning segment has increased by 18%. This adaptation of the functioning intestine after jejunoileal bypass is responsible for the slow gain of weight after an initial loss of weight and is one of the factors contributing to the ultimate result of loss of weight by jejunoileal bypass.
One week after a 4+2 cm jejunoileal bypass the length of the functioning segment has not yet increased whereas after 2 weeks actually a 9% shortening occurs.
In contrast, the thickness of the entire wall of functioning jejunum increases by 8% after 1 week and by 33% after 2 weeks. The thickness of the entire wall of functioning ileum increases even more, by 69% after 1 week and by 79% after 2 weeks.
A 10% jejunoileal bypass induces a stronger adaptation of the functioning segment than a 4+2 cm bypass, which is essentially a 7% bypass.
The functioning jejunum and ileum show a hypertrophic pattern according to the classification by Lee (1980).
After construction of a 4+2 cm jejunoileal bypass it takes one

to two weeks before atrophy of the excluded intestine starts to become visible and after 16 weeks atrophy occurs in all cases.
The thickness of all intestinal layers of the excluded jejunum shows only minor changes : a slight decrease in crypt height and a slight increase in muscularis propria after 2 and 16 weeks.
The thickness of the entire wall of the excluded distal ileum increases by 26% 1 week after 4+2 cm jejunoileal bypass and after 2 weeks by 41%. After 16 weeks a 6% increase, as compared to the peroperative level, remains.
The increases, measured after 1 and 2 weeks, are to be attributed to villous height and thickness of muscularis propria while after 16 weeks villous height has been reduced to the value at operation and crypt height has decreased by 4%.
These changes in excluded jejunum and excluded ileum after 16 weeks fit the hypoplastic pattern in Lee's classification (1980).
The increase of thickness of muscularis propria in the excluded jejunum and ileum seems to correspond with the frequently observed abdominal cramps and bypass enteritis which sometimes complicates jejunoileal bypass in patients.
The macroscopic aspect of the excluded segment, that is the occurrence of either much or little atrophy, shows no clear relationship with the microscopic measurements of the excluded segments.
Macroscopic reflux into the excluded distal ileum only finds minor expression in the microscopic measurements of the distal ileum.
In the portacaval shunt rats a striking, but not clearly significant, increase of muscularis propria is found in both the jejunum (21%) and the ileum (32%) 16 weeks after construction of the shunt.

HEPATIC HISTOLOGY

7.1 Introduction

One of the most feared and serious complications of jejunoileal bypass in man is hepatic dysfunction.
As early as 1972 McGill reported a fatal case of liver failure after jejunoileal bypass.
O'Leary (1976) estimated the degree of hepatic involvement at 43% of the patients after bypass, while Halverson (1978) found a 7% incidence of liver failure with a 50% mortality.
This liver failure usually occurs in the first 18 months after bypass, corresponding to the period of rapid loss of weight.
After 18 months an adaptive process occurs and liver histology improves (Marubbio, 1976; Salmon, 1975).
Liver biopsies at the time of construction of jejunoileal bypass showed three characteristics in most morbidly obese patients : fatty infiltration, portal fibrosis and portal infiltrates.
Fatty infiltration of the liver was found in 68% to 94% of the patients (Kern ,1973, 1974; Marubbio, 1976, 1979).
The distribution of fat was centrilobular or panlobular but not periportal.
Portal fibrosis was found in 10% to 28% of the patients and portal infiltrates, predominantly round cell infiltrates, were seen in 20% to 58%.
After 1 year liver biopsies showed increases of these three characteristics and in some patients Mallory's hyaline appeared either in the periportal area or in the central area (Kern, 1973, 1974; Marubbio, 1976, 1979).
Relatively few experiments concerning effects of jejunoileal bypass on liver morphology in animals have been reported. Some work has been done with dogs (McClelland, 1970; O'Leary, 1974),with lean rats (Vanderhoof, 1979 and 1980) and with obese rats (Madura, 1975; Grosfeld, 1976).
The fat Zucker rat shows a characteristic hypertrophy of the liver. This hypertrophy is caused by fatty infiltration of the liver (Madura, 1975; Grosfeld,1976).
Thus, the Zucker rat offers a suitable model to study effects on liver morphology after jejunoileal bypass since its liver morphology is similar to that of the morbidly obese patient.
Enhanced deposition of iron in the liver of rats after portacaval shunting has been reported by Kaplan (1966).

7.2 Anatomy of the liver

A short description of the anatomy of the liver will be given,in order to clarify the terms which will be used

throughout this chapter.
For the assesment of two-dimensional sections it appears convenient to use the long established lobular concept of the liver by which each unit consists of cords of liver cells radiating from the central vein to peripheral portal tracts.
Each radiating plate consists of hepatocytes one cell thick and merges with similar limiting plates which border upon portal tracts and hepatic veins. Separating these plates are the liver sinusoids along which blood flows from portal tracts to central veins (Patrick and McGee, 1980).
The liver is a highly vascularized organ which receives afferent blood from both the portal vein (75%) and the hepatic artery (25%).
Since blood flows from the portal canals into the liver lobule and through the sinusoids to the central vein, a lobular gradient concept has been postulated for the uptake of certain substances.Indeed, a number of studies, concerning glycogen and lipid deposition after meals and pathological changes after the administration of hepatotoxins, have demonstrated metabolic differences in parenchymal cells along a lobular gradient. Furthermore, morphometric analyses have shown that centrilobular hepatocytes contain different volumes of specific organelles, e.g. an increased volume of smooth endoplasmatic reticulum and less mitochondria, as compared to parenchymal cells nearer the portal vessels (Jones, 1977).
Therefore, examining steatosis and siderosis in the liver, we have made a differentiation in a pericentral or centrilobular zone, a periportal zone and a mid-zone, between the pericentral and periportal zone.

7.3 Method

At operation liver biopsies were taken from all rats (3.2.9).
Sixteen weeks later a further liver biopsy was taken under the same anesthetic conditions.
In rats expiring within this period a liver biopsy was also taken except in those animals which died during or shortly after operation as a result of anesthetic problems.
The biopsy specimens were immediately fixed in a 4% formaldehyde solution for routine processing and stained with hematoxylin-eosin, periodic acid-Schiff, Azan and Perls.
Steatosis was recorded for the pericentral area,the mid-zonal area between pericentral and periportal areas, and the periportal area.
For each area a scale between zero and four was used : no identifiable intracellular fat rated 0, minimal steatosis rated as 1, mild steatosis rated 2, moderate steatosis rated 3 and marked steatosis rated 4 (Salmon and Reedijk, 1975).
The presence of iron in Perls's staining procedure (siderosis) was recorded similarly.
Degeneration of liver cells was classified by 4 parameters : the presence of Councilman bodies, of inflammatory or mononuclear infiltration of the portal triad, of Mallory bodies and of degeneration of groups of liver cells.
Again a scale was used ranging from zero, indicating absent, to four, indicating markedly present.

7.4 Steatosis of the liver

7.4.1 Steatosis of the liver at operation

Steatosis or fatty change is defined as light microscopically visible fat in the liver. Steatosis is the most common form of hepatocyte degeneration, especially the type with large cytoplasmic droplets of fat and displacement of cell nuclei. Also, fat droplets from neighbouring cells may coalesce to a large fatty cyst which lies extracellularly and produces an inflammatory reaction (Poulsen, 1979).
Table 7.1 shows localization and degree of steatosis of the liver at operation in 59 male and female fatty Zucker rats.

steatosis	*sham*	*4+2 cm*	*10%*	*p.c.s.*	*total*
pericentral					
none			*2*		*2*
minimal	*1*	*1*			*2*
mild	*4*	*5*	*9*	*2*	*20*
moderate	*2*	*4*	*3*	*3*	*12*
marked	*3*	*7*	*8*	*5*	*23*
mid-zonal					
none			*1*		*1*
minimal					*0*
mild	*2*	*1*	*1*	*1*	*5*
moderate	*3*	*6*	*7*		*16*
marked	*5*	*10*	*13*	*9*	*37*
periportal					
none	*1*		*5*	*2*	*8*
minimal	*1*				*1*
mild	*4*	*8*	*5*		*17*
moderate	*2*	*3*	*2*	*2*	*9*
marked	*2*	*6*	*10*	*6*	*24*
diffuse	*5*	*9*	*8*	*5*	*27*
not diffuse	*5*	*8*	*13*	*5*	*31*
not present	*0*	*0*	*1*	*0*	*1*
N	*10*	*17*	*22*	*10*	*59*

Table 7.1 Steatosis of the liver at operation. Localisation and degree of steatosis in fatty Zucker rats, differentiated into the 4 experimental groups. N is number of rats.

Diffuse distribution of steatosis means that steatosis is present in each of the 3 locations and to the same degree.
Only 1 rat (in the 10% bypass group) proves to be free of

steatosis of the liver.
In 46% of the rats (27 of 59) steatosis appears to be equally distributed over the 3 liver areas.
The number of rats showing marked steatosis is clearly greater than the number of rats with a milder degree of steatosis. Marked steatosis shows a mid-zonal preponderance of 63% (37 out of 59 rats) of the rats compared with the pericentral area, 39% (23 out of 59 rats), and the periportal area, 41% (24 out of 59 rats).
This situation in fatty rats is not entirely similar to that in man as reported by Poulsen (1978). He finds mostly a diffuse distribution or a centrilobular preponderance, while a predominantly periportal steatosis is rare and a predominantly mid-zonal steatosis is extremely rare.

7.4.2 Steatosis of the liver 16 weeks after operation

In order to evaluate the effect of a sham operation, a 4+2 cm jejunoileal bypass, a 10% jejunoileal bypass and a portacaval shunt on steatosis of the liver, degree and localization of steatosis were again classified at sacrifice after 16 weeks.
For each localization the number of rats was recorded with either a decreased, an increased or an unchanged degree of steatosis.
Results are given in table 7.2.

steatosis	*sham*	*4+2 cm*	*10%*	*p.c.s*
pericentral				
decrease	5	15	18	8
no change	3	2	3	2
increase	2	0	1	0
mid-zonal				
decrease	4	14	17	9
no change	6	2	4	1
increase	0	1	1	0
periportal				
decrease	5	14	13	8
no change	3	3	7	1
increase	2	0	2	1
total	10	17	22	10

Table 7.2 Number of rats showing a changed steatosis of the liver 16 weeks after operation as compared to steatosis at operation.

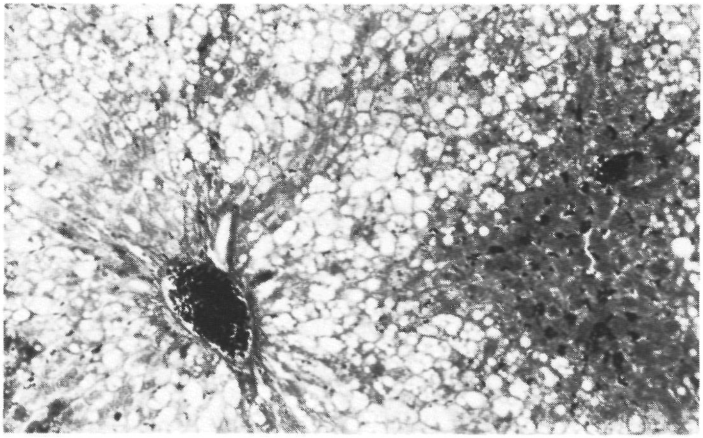

Fig. 7.1. Marked steatosis of the liver in the fat Zucker rat at operation. (Azan: x 104).

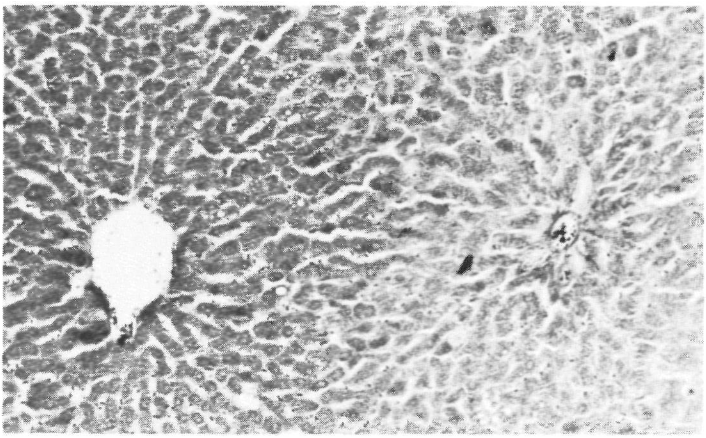

Fig. 7.2. Liver at autopsy 16 weeks after 10% jejunoileal bypass. Minimal steatosis. (Azan: x 104).

It is obvious that in the 4+2 cm and the 10% bypass as well as in the portacaval shunt group a majority of the rats show a general decrease of steatosis.
This effect is clearly less in the sham group.
This observation can be statistically supported by the employment of a sign test, which compares the number of rats showing a decrease of steatosis with the number of rats showing an increase of steatosis.
Then the sham group shows no significant change of degree of steatosis in any of the 3 liver areas. The 4+2 cm bypass group, the 10% bypass group and the portacaval shunt group, however, all show a significant decrease of degree of steatosis after 16 weeks in all 3 liver areas ($p \leq 0.001$, $p \leq 0.01$ and $p \leq 0.05$ for the groups, respectively).
In order to find differences in change of steatosis among the 4 experimental groups and to localize the area in the liver in which most rats show a decrease of steatosis we have employed a Kruskal-Wallis test and next a Wilcoxon test.
When we compare the sham group with the 4+2 cm bypass group the number of rats with a decreased pericentral steatosis is significantly greater in the 4+2 cm group ($p = 0.02$).
The same holds good for the mid-zonal decrease ($p = 0.04$), while the difference between the two groups in periportal decrease is nearly significant ($p = 0.056$).
When we compare the sham and the 10% group as to the pericentral and mid-zonal decrease of steatosis these figures show the same tendency , with $p = 0.060$ and $p = 0.062$ respectively, whereas periportal decrease is not different ($p = 0.52$).
When we compare the sham and the portacaval shunt group, only the mid-zonal decrease is greater for the portacaval shunt group ($p = 0.02$).

7.4.3 Steatosis of the liver 1 week, 2 weeks and 16 weeks after 4+2 cm jejunoileal bypass

Salmon and Reedijk (1975) have reported increasing steatosis in the early postoperative period following jejunoileal bypass in man with a direct correlation between the rate of loss of weight and fatty metamorphosis. By 1,000 days postoperatively they observed disappearance of fat, a phenomenon also reported 2 years after bypass by Kern et al. (1974).
Therefore we have studied the change of steatosis of the liver in Zucker rats killed 1 week, 2 weeks and 16 weeks after 4+2 cm jejunoileal bypass.
Table 7.3 shows the decrease, steady state or increase of steatosis in the liver at various times after operation compared with the level at operation.

steatosis	1 week	2 weeks	16 weeks
pericentral			
decrease	0	4	15
no change	5	2	2
increase	0	0	0
mid-zonal			
decrease	0	2	14
no change	5	4	2
increase	0	0	1
periportal			
decrease	0	1	14
no change	5	1	3
increase	0	4	0
N	5	6	17

Table 7.3 Number of rats showing change of steatosis in various liver areas 1 week, 2 weeks and 16 weeks after 4+2 cm jejunoileal bypass.

Evidently, 1 week after jejunoileal bypass steatosis has not yet changed. After 2 weeks the changes in steatosis are too erratic for any conclusions to be drawn and a sign test does not show any significance. Steatosis after 16 weeks has been dealt with in 7.4.2 .

7.5 Siderosis of the liver

7.5.1 Siderosis of the liver at operation

The presence of stainable iron in tissue is called siderosis. It is most common in liver cells and/or Kupffer cells. Iron is bound in the cells as hemosiderin, which is a complex with variable quantities of carbohydrates, proteins and iron.The iron is in a trivalent state and gives a positive Prussian blue reaction in Perls's staining procedure.

Iron containing pigment in Kupffer cells alone is most typically seen in acute hepatitis (Poulsen, 1979).

About 50% of the biopsies from his patients with acute hepatitis show iron containing pigment in Kupffer cells and portal macrophages.

In table 7.4 localization and degree of siderosis of the liver at operation is given in 59 fatty Zucker rats,divided according to the 4 experimental groups.

siderosis	sham	4+2 cm	10%	p.c.s.	total
pericentral					
none	10	16	21	10	57
minimal			1		1
mild		1			1
mid-zonal					
none	10	17	21	10	58
minimal			1		1
periportal					
none	10	17	21	10	58
minimal			1		1
diffuse			1		1
not diffuse		1			1
not present	10	16	21	10	57
N	10	17	22	10	59

Table 7.4 Siderosis of the liver at operation. Localization and degree of siderosis in fatty Zucker rats in the 4 experimental groups. N is number of rats.

Table 7.4 clearly shows that in only one rat minimal siderosis is present in all zones, while in another rat mild siderosis is present in the pericentral zone of the liver.
Siderosis has been found in the Kupffer cells.

7.5.2 Siderosis of the liver 16 weeks after operation

For the purpose of evaluating the effect of a sham operation, a 4+2 cm jejunoileal bypass, a 10% jejunoileal bypass and a portacaval shunt, on siderosis of the liver, degree and localization of siderosis were again classified at sacrifice after 16 weeks.
For each localization the number of rats was recorded with either decreased, an increased or an unchanged degree of siderosis.
Results are given in table 7.5.

siderosis	sham	4+2cm	10%	p.c.s.
pericentral				
no change	7	9	9	0
increase	3	8	13	10
mid-zonal				
no change	7	14	13	1
increase	3	3	9	9
periportal				
no change	7	14	15	1
increase	3	3	7	9
total	10	17	22	10

Table 7.5 Number of rats showing a changed siderosis of the liver 16 weeks after operation as compared with siderosis at operation.

Decrease of siderosis has not been found in any group for any location.
When we apply a sign test, the increases in siderosis in the sham group are not significant. In the 4+2 cm bypass group the increase is only significant in the pericentral zone ($p < 0.01$) and in both the 10% bypass group and the portacaval shunt group the increase is significant in all three zones ($p \leq 0.02$).
When we compare each experimental group with each one of the other 3 groups, at the same time considering the localization of siderosis, the portacaval shunt group shows an increased siderosis in all areas if compared with the sham group ($p < 0.008$, Kruskal-Wallis and Wilcoxon tests).
The same holds good when we compare the portacaval shunt group and the 4+2 cm bypass group ($p < 0.006$) and when we compare the portacaval shunt group and the 10% bypass group ($p < 0.02$).
Neither the 4+2 cm bypass group nor the 10% bypass group shows any increased siderosis in comparison with the sham group.
Thus, siderosis of the liver does not change in the sham group ; in the 4+2 cm bypass group siderosis only increases in the pericentral zone and in the 10% bypass group siderosis increases in all zones, especially in the pericentral zones; in the portacaval shunt group siderosis nearly always increases and does so in all zones, especially in the pericentral zone.
The pericentral zone appears to be the zone of predilection

for siderosis of the liver.

7.5.3 Siderosis of the liver 1 week , 2 weeks and 16 weeks after 4+2 cm jejunoileal bypass

In 5 rats, killed 1 week after 4+2 cm jejunoileal bypass and in 6 rats, killed 2 weeks after 4+2 cm jejunoileal bypass siderosis was absent both at operation and after 1 or 2 weeks. Therefore siderosis in the pericentral area, as seen in the 4+2 cm jejunoileal bypass group after 16 weeks, does not develop within 2 weeks after construction of the bypass.

7.6 Degeneration of liver cells

7.6.1 Degeneration of liver cells at operation

Degeneration of liver cells was classified according to the presence of the following parameters : Councilman bodies, inflammatory or mononuclear infiltration of the portal triad, Mallory bodies and degeneration of groups of liver cells.
A Councilman body is a sign of acidophilic liver cell degeneration.
It is found in a hepatocyte which is shrunken but conspicuous because of the intense eosinophilic staining of its cytoplasm.
A Mallory body is a sign of hyaline degeneration. The cytoplasm of the affected hepatocyte contains hyaline bodies (Mallory bodies) of rounded or irregular shape which may not be clearly defined.
There is a common association with alcoholic hepatitis, especially in the centrilobular hepatocytes (Patrick and McGee, 1980).
The presence of the parameters was rated as zero, minimal, mild, moderate and marked.
Table 7.6 shows the presence of parameters of degeneration of the liver in the 4 experimental groups at operation .

degeneration of the liver	*sham*	*4+2 cm*	*10%*	*p.c.s.*
Councilman bodies	*1*	*1*	*5*	*1*
inflammation portal triad	*1*	*4*	*6*	*0*
Mallory bodies	*1*	*1*	*1*	*0*
Number of rats	*10*	*20*	*23*	*10*

Table 7.6 Number of rats showing degeneration of the liver at operation. In all cases the degree of degeneration is mild.

Degeneration of groups of liver cells has not been found.
In all cases the degree of degeneration is mild.
In the sham, 4+2 cm bypass and 10% bypass group each, only 1 rat is to be found with a mild degeneration of the liver as indicated by the presence of 3 parameters.
Thus, liver degeneration in 63 fatty Zucker rats is hardly present and ,if present, only in a mild form.

7.6.2 Degeneration of liver cells 16 weeks after operation in 4 experimental groups and 1 week, 2 weeks and 16 weeks after a 4+2 cm jejunoileal bypass

The 4 parameters indicating degeneration of liver cells neither show significant improvement nor deterioration in any of the 4 experimental groups after 16 weeks (sign test).
Though one might expect deterioration of the liver shortly after construction of a jejunoileal bypass, which has been reported in man, neither of the 4 parameters supposedly reflecting degeneration of the liver shows any change at 1 week, 2 weeks and 16 weeks after construction of a 4+2 cm jejunoileal bypass (sign test).
Thus, no signs of enhanced liver degeneration could be demonstrated after sham operation, jejunoileal bypass or portacaval shunt in fatty Zucker rats.

7.7 Discussion

Hepatic disease is the most serious complication after jejunoileal bypass for morbid obesity.
Biopsies of the liver in man show alterations of liver cells identical to that observed in alcoholic liver disease suggesting a similar etiology.
Histologic changes include increase of fatty degeneration in the early postoperative period, increase of portal infiltrates and fibrosis, and central pericellular fibrosis as a precursor of micronodular cirrhosis (Marubbio, 1979).
McGill (1972) and Peters (1975) describe patients who develop Mallory bodies after jejunoileal bypass. In those patients who die of hepatic failure , cirrhosis, focal necrosis, cholestasis and Mallory's hyaline have been found.
Holzbach (1974) has analyzed the lipid content of the liver in morbid obesity. He found increased levels of triglyceride, whereas phospholipid, cholesterol esters and free cholesterol levels were normal.
Grosfeld (1977) reports that total hepatic lipids, hepatic triglycerides and hepatic synthesis of fatty acids were significantly elevated in fat Zucker rats as compared with lean Zucker rats, whereas a 10% jejunoileal bypass had little effect in reducing elevated hepatic lipids, triglycerides and fatty acid synthesis as measured 4 weeks after operation. Serum triglycerides decreased.
Our results are partly in contrast with these findings since serum triglyceride decreases in 7% jejunoileal bypass as well as in 10% jejunoileal bypass after 7 weeks and after 16 weeks, whereas fatty degeneration of the liver, which is mostly due to an increased level of hepatic triglyceride, improves after jejunoileal bypass.

This discrepancy might be explained by the time elapsed since operation : 4 weeks versus 7 or 16 weeks, respectively.
For Holzbach (1974) found in man an increase of hepatic triglyceride 1 year after bypass, so still in the weight-reducing period.
The etiology of the process that produces the liver changes after jejunoileal bypass is as yet poorly understood.
At present two theories prevail. One theory incriminates malnutrition as the main cause (Moxley, 1974), while the other suggests that a toxin is released from the excluded small intestine (O'Leary, 1974).
Other explanations include choline deficiency (Nolan, 1968), an altered bile metabolism (Sherr,1974) and an endogenous ethanol production (Mezey, 1975).
The endotoxin theory is supported by the investigations of McClelland (1970), O'Leary (1974), Vanderhoof (1979) and Kaminsky (1980).
Liver failure could be prevented by supplemental feeding or with antibiotics in the excluded bowel, fixed at the abdominal wall as a fistula.
Overgrowth of anaerobic bacteria, especially bacteroides, was demonstrated in the excluded bowel of dogs and when death occurred it was always due to liver failure. Treatment with antibiotics prevented death and reduced fat deposition.
Against this theory bears up the negative result of a randomized clinical study in which half of the patients received doxycycline after jejunoileal bypass (Yost, 1979).
Protein malnutrition appears to offer the most satisfactory explanation although Lockwood (1977) failed to suppress liver abnormalities after bypass surgery with oral peptide supplementation. He attributed this to inadequate intestinal absorption.
Marescaux (1981) supports this suggestion by correlating hepatic dysfunction to morphological and enzymatic adaptation of the functioning intestine in the rat.
In the period of impaired liver function he observed a period of selective adaptation of maltase and sucrase activities, whereas there was no increase of aminopeptidase activity in the brush borders of the functioning ileal part of the shunt.
This resulted in a preferential absorption of carbohydrates along with a protein deficiency and thus in an impaired nutritional status similar to kwashiorkor.
An additional argument supporting the role of protein malnutrition is the reversal of hepatic steatosis in intestinal bypass patients by intravenous infusion of calorie-free aminoacids (Heimburger, 1975, Ames, 1976).
In the literature about liver failure after jejunoileal bypass reduction of blood flow to the liver is never mentioned.
Pector (1980) found that the total hepatic blood flow in rats had been reduced after portacaval shunt and that the wet weight of the liver had decreased by 43%. In a study of the contrasting effects of portacaval shunt and portacaval transposition on fatty acid and cholesterol biosynthesis in the rat liver it appeared that the reduction of fatty acids and cholesterol in the liver of rats with portacaval shunt was to be attributed to the reduction of total hepatic blood flow

rather than to the diversion of portal constituents.
Since the blood flow of the liver is maintained by the portal vein for 75% and by the hepatic artery for 25% it is obvious that an end-to-side portacaval shunt must cause a strong reduction of the liver blood flow.
One can imagine that the extent of adaptation through increase of flow in the hepatic artery keeps liver blood flow on a marginal but viable level after portacaval shunt.
The inflow of blood into the portal vein is greatly dependent on the outflow and vascular resistance of the intestine and, to a smaller extent, of the spleen (Richardson, 1981).
This means that bypassing 90% of the small intestine causes approximately 67% reduction of total liver flow. Apart from this steady state, a postprandial hyperemia is known to occur, resulting in an increase in blood flow ranging from 28% to 132% through the superior mesenteric artery (Granger, 1980).
A major portion of the " resting" blood flow is distributed to the mucosa-submucosa. Within the mucosa-submucosa 5-53% of total wall flow is generally attributed to the submucosa whereas the villi and crypts account for 24-37% and 21-27% of total intestinal blood flow respectively.
Bond (1979) showed that in the conscious dog 45 minutes after ingestion of a high-protein meal blood flow to the whole wall of the body of the stomach, jejunum and ileum increased by 96%,93% and 153% respectively.
Villi, crypts, submucosa and muscularis equally shared in the enhanced postprandial flow.
Therefore, it might well be that the reduction of total hepatic blood flow after a meal in a patient with a 10% jejunoileal bypass is considerably greater than 67% , which supposedly occurs postprandially, than in a patient without a bypass.
Touloukian (1971,1972) resected the middle half of the gut in rats leaving equal jejunal and ileal remnants. The ileal remnant hypertrophied within 2 months and was comparable in weight to the entire ileum of control rats. The jejunal remnant showed no hypertrophy and blood flow remained approximately one half of that of control rats.
The mucosal blood flow of the ileal remnant was markedly greater than the controls 2 days after resection but returned to values similar to the controls 2 months after resection, thus demonstrating adaptation.
So, we suggest that a reduction of blood flow in the functioning intestine, and thus to the liver, may play a role in the etiology of liver failure after jejunoileal bypass.

7.8 Summary

The fat Zucker rat is characterized by steatosis of the liver with a preponderance in the mid-zonal area. There is no siderosis of the liver while degeneration of liver cells is almost completely absent and if indeed present, only in a mild form.
No changes in degeneration of liver cells occur during the first two weeks after a 4+2 cm jejunoileal bypass.
Sixteen weeks after operation the sham group shows no changes

in the liver.
The 4+2 cm bypass rats show significant reduction in steatosis of the liver in the pericentral zone, the periportal zone and the zone between the pericentral and periportal area. Siderosis of the liver only increases in the pericentral zone, whereas degeneration of the liver cannot be demonstrated.
The 10% jejunoileal bypass rats show significant reduction in steatosis of the liver in the pericentral and mid-zonal area. Siderosis increases in all areas, especially in the pericentral area. Degeneration of the liver cannot be demonstrated.
The portacaval shunt rats show significant reduction in steatosis of the liver in the mid-zonal area. Siderosis increases in all areas, especially the pericentral area. This increase of siderosis in the portacaval shunt rats is significantly greater than in the two groups with jejunoileal bypass.
Degeneration of the liver cannot be demonstrated.
Analogous to the reduction of blood flow to the liver in a portacaval shunt, reduction of blood flow to the liver in a jejunoileal bypass is postulated as one of the factors contributing to liver disease after jejunoileal bypass.

Chapter 8

CECOMEGALY

8.1 Introduction

It has already been mentioned (3.1) that enormous distension of the cecum was found after jejunoileal bypass in our pilot study. One rat died through volvulus of the enlarged cecum. Both this enormous distension of the cecum, called cecomegaly, and mortality due to volvulus of the cecum was already observed by Gustafsson in 1946 in germfree rats (Gustafsson, 1959).

On account of the results of the pilot study a relation was expected between cecomegaly and jejunoileal bypass. Also, one might expect a link between cecomegaly and bacterial flora of the cecum. Therefore, we investigated the size of the cecum in the four experimental groups and the cecal microflora in a limited number of rats.

8.2 Anatomy of the cecum in the rat

The cecum in the rat forms a more or less distended pocket, 2 to 4 cm long, in which the feces accumulate.

It includes a lower part into which the ileum opens at the level of a fold which forms a true ileocecal valve, and which is continuous with the ascending colon at the level of this valve. The upper distal part of the cecum, slightly separated from the previous part by a narrowed area, is pointed at its extremity. Its wall includes many areas of lymphatic tissue and functionally it corresponds to the human appendix. The wall of the cecum is very thin and fragile (Lambert, 1965). The cecum, as part of the colon, has no villi. Its wall consists of crypts (nearly identical with the total mucosal layer), muscularis mucosae, submucosal layer, muscularis propria, subserosa and a serosal layer (see fig.8.1).

8.3 Cecal size at operation and 2 weeks and 16 weeks after operation

At operation the length of the cecum was measured both along the mesenteric and the antimesenteric border (see 3.3.1). The sum of both values was taken as the circumference of the cecum.

Table 8.1 gives the results of the measurements of the cecum in the 4 experimental groups at operation.

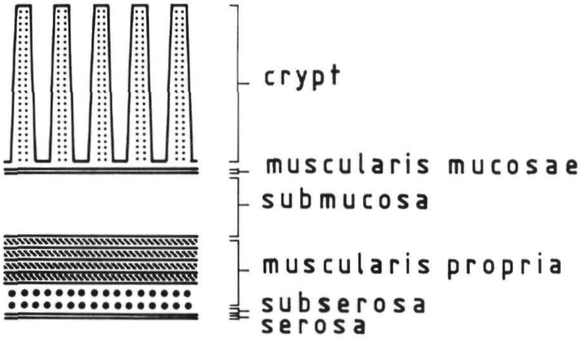

Fig. 8.1. Schematic anatomy of the cecum of the fat Zucker rat.

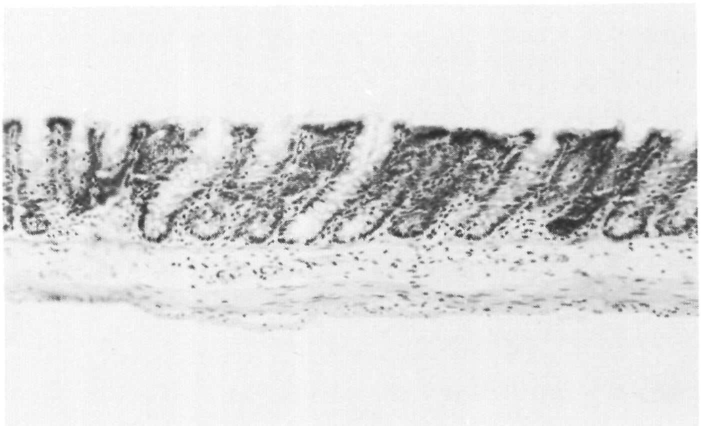

Fig. 8.2. Cecum of the fat Zucker rat 16 weeks after a sham operation.
(H.E. : x 26).

cecum	sham	4+2 cm	10%	p.c.s.
mesenteric part	23 ± 5	26 ± 4	23 ± 3	24 ± 3
antimesenteric part	50 ± 12	52 ± 9	47 ± 7	58 ± 5
circumference	73 ± 16	78 ± 11	71 ± 8	82 ± 7
N	10	20	23	10

Table 8.1 Size of cecum at operation : the circumference is calculated as the sum of the mesenteric and antimesenteric parts. Results are expressed in mm ± s.d.. N is number of rats.

The length of the antimesenteric part of the cecum is about twice the length of the mesenteric part. In the portacaval shunt group the circumference of the cecum is larger, probably on account of older age of the animals. Sixteen weeks after operation the cecum was measured again. These values are compared with the measurements at operation and the average changes for each experimental group are given in table 8.2 .

	N	Δ mesent.part	Δ antimes.part	Δ circumference
sham	10	5 ± 6 (20%)	18 ± 14 (35%)	22 ± 19 (30%)
4+2 cm	20	8 ± 6 (33%)	49 ± 15 (93%)	57 ± 18 (73%)
10%	23	9 ± 5 (38%)	41 ± 18 (86%)	49 ± 21 (70%)
p.c.s.	10	-0.2 ± 5 (1%)	2 ± 13 (4%)	2 ± 14 (3%)

Table 8.2 Increase in size (= Δ) of the cecum 16 weeks after operation in 4 experimental groups. The circumference is calculated as the sum of the mesenteric and antimesenteric parts. Results are expressed as average increase (in mm) ± s.d. and, between brackets, as percentual increase.

The cecal circumference in the sham group is enhanced by 30%, which is highly significant ($p = 0.006$, Student's paired test). Both the 4+2 cm and the 10% jejunoileal bypass show a highly significant increase of the cecal circumference (73% and 70% respectively, $p < 0.001$).
The p.c.shunt group shows no change in cecal circumference after 16 weeks. In the other three groups both the mesenteric and the antimesenteric part of the cecum increase

significantly, the antimesenterial part even more than the mesenterial side. If we employ a one-way analysis of variance and the simultaneous multiple comparison method of Scheffè the cecal circumference of the 4+2 cm and 10% jejunoileal bypass rats increases significantly in comparison with the sham rats ($p = 0.0002$ and $p = 0.004$ respectively).
The increase of cecal circumference in the p.c. shunt group does not significantly differ from that in the sham group. Nor does there exist any difference in increase of cecal circumference between the 4+2 cm and 10% jejeunoileal bypass groups. Exactly the same holds good for the antimesenteric part of the cecum.
The mesenteric part of the cecum only shows significant increase if we compare the p.c.shunt group with the 4+2 cm jejunoileal bypass and with the 10% jejunoileal bypass groups. Thus cecomegaly clearly occurs 16 weeks after 4+2 cm jejunoileal bypass (which actually is a 7% jejunoileal by-pass) and after 10% jejunoileal bypass.
Portacaval shunt causes no cecomegaly.
Six rats were killed 2 weeks after 4+2 cm jejunoileal bypass. Table 8.3 compares the changes in length of the cecal parts, as measured 2 weeks and 16 weeks after operation.

4+2 cm killed	*N*	*Δ mesent.part*	*Δ antimes.part*	*Δ circumference*
2 weeks	*6*	*10 ± 7 (38%)*	*20 ± 20 (39%)*	*30 ± 25 (39%)*
16 weeks	*20*	*8 ± 6 (33%)*	*49 ± 15 (93%)*	*57 ± 18 (73%)*

Table 8.3 Increase in size (= Δ) of the cecal parts 2 weeks and 16 weeks after 4+2 cm jejunoileal bypass.
Results are expressed as average increase (in mm) ± s.d. and, in brackets, as percentual increase.

After 2 weeks the increase of the length of the mesenteric part of the cecum is 38% which is significant compared with the value at operation ($p = 0.02$, Student's paired test). The antimesenteric part increases by 39% which is almost significant ($p = 0.06$), whereas the circumference significantly increases by 39% ($p = 0.03$).
If we compare the results in the sham group (table 8.2) with those in the 4+2 cm bypass group killed after 2 weeks and 16 weeks (table 8.3), the increase in length of the mesenteric part of the cecum is not significantly different in these 3 groups. The increase in length of the antimesenteric part of the cecum is only significant in the 4+2 cm bypass group after 16 weeks. The same holds good for the increase of circumference of the cecum (analysis of variance and simultaneous multiple comparison method of Scheffè).
Thus, cecomegaly is not yet present 2 weeks after 4+2 cm

jejunoileal bypass. Therefore cecomegaly takes more than 2 weeks to develop after jejunoileal bypass.

8.4 Microscopic measurements of the cecal wall

The cecal wall was examined in a group of fat Zucker rats with a 4+2 cm jejunoileal bypass sacrificed after 2 weeks and in the 4 experimental groups 16 weeks after operation. No biopsies of the cecum were taken at operation, so all measurements have to be compared with those of the sham group 16 weeks postoperatively.
After fixation, sectioning and staining of the cecal specimens by a procedure similar to that used for the specimens from the small intestine, crypt height, thickness of muscularis propria and thickness of the entire cecal wall were measured. The results are given in table 8.4.

	N	*crypt*	*musc.prop.*	*entire wall*
sham	*10*	*217 ± 90*	*111 ± 38*	*405 ± 149*
4+2 cm	*20*	*220 ± 51*	*103 ± 41*	*388 ± 110*
10%	*23*	*224 ± 54*	*124 ± 45*	*420 ± 94*
p.c.s.	*10*	*190 ± 35*	*127 ± 43*	*364 ± 74*
2 weeks				
4+2 cm	*6*	*230 ± 35*	*121 ± 36*	*391 ± 50*

Table 8.4 Crypt height, thickness of muscularis propria and thickness of the entire wall of the cecum (in μ ± s.d.) in the 4 experimental groups 16 weeks after operation and in 4+2 cm jejunoileal bypass 2 weeks after operation. N is number of rats.

Analysis of variance shows no differences between the sham group and the other 4 groups.
This result appears to be contradictory to the development of unmistakable cecomegaly in the 10% bypass group and the 4+2 cm bypass group as measured 16 weeks after operation.

8.5 Cecal weight, bacterial counts and bacterial cultures. Gastro-intestinal transit time

In order to analyse the effect of jejunoileal bypass on the bacterial content in the cecum and on the gastro-intestinal transit time, 10 rats were operated upon and kept in individual metabolic cages.
We tried to measure gastro-intestinal transit time according to Koopman and Kennis (1977).
The method is based on feeding 20 minute steel balls and subsequent x-ray examination of sequentially collected feces.
However, since the steel balls were retained in the enlarged cecum the quantitative recovery of carminic acid dye in the

feces, following intragastrical application, was applied (Koopman, 1977).
This method yielded such divergent results that no conclusions were possible. One of the interfering factors may be the dye being retained in the enlarged cecum, another factor was coprophagia in spite of the metabolic cages.
In order to study the cecal microflora an additional 5 rats with a 4+2 cm jejunoileal bypass were sacrificed after 1 week. Each cecum was homogenized under strictly anaerobic conditions (Koopman, 1977). Serial tenfold dilutions were made and microscopic bacterial counts were performed on gram-stained slides, yielding total bacterial count.
After an incubation period of 7 days the cultured bacteria were counted in the same way, yielding the viable bacterial count, consisting of anaerobic and aerobic bacteria. Regrettably, both total bacterial counts and viable bacterial counts were too divergent in all groups for us to reach any significant conclusion.
Table 8.5 shows the cecal weight and the relative cecal weight (in percentage of the total body weight) in sham rats, 4+2 cm and 10% jejunoileal bypass rats, killed after 16 weeks, and in 4+2 cm jejunoileal bypass rats, 1 week after operation.

	N	*cecal weight*	*relative cecal weight*
sham	*3*	*2.5 ± 0.4 g*	*0.7 ± 0.1%*
4+2 cm	*4*	*6.2 ± 1.5 g*	*2.5 ± 0.4%*
10%	*3*	*5.2 ± 2.0 g*	*2.1 ± 1.4%*
4+2 cm			
1 week	*5*	*2.4 ± 0.4 g*	*0.7 ± 0.1%*

Table 8.5 Cecal weight (mean in g ± s.d.) and relative cecal weight (mean in % of body weight ± s.d.) in rats with a sham operation, or a 4+2 cm or a 10% jejunoileal bypass, killed after 16 weeks, and in rats with a 4+2 cm jejunoileal bypass killed after 1 week. N is number of rats.

If we employ an analysis of variance and subsequently the simultaneous multiple comparison method of Scheffé, cecal weight 1 week after 4+2 cm jejunoileal bypass proves to be the same as in the sham group.
However, 16 weeks after 4+2 cm jejunoileal bypass it is significantly greater than in the sham group (p = 0.01) whereas 16 weeks after a 10% jejunoileal bypass it is also enhanced, though not significantly (p = 0.098).

8.6 Discussion

Cecomegaly has been observed in rodents which were kept germfree. It has not been observed in the dog, the cat, the pig nor in ruminants.
Schedl (1974) found hypertrophy of the cecum in diabetic hyperfagic rats.
Peters (1972) gives 4 methods of bringing about cecomegaly in experimental animals : by excessive feeding with rough cellulose (± 80%), by orally administering large doses of antibiotics, by feeding guinea pigs a sterilised diet and by rearing rodents in a germfree way.
The relative cecal weight (cecal weight in percentage of body weight) is approximately 10% in germfree rats and 1% to 2% in conventional rats.
The cecal circumference increases fivefold in the germfree rat whereas the empty weight of the cecum increases by 50% in comparison with conventional rats. This means that the cecal wall decreases in thickness. The cecal mucosa in germfree rats is only 30% of that in conventional rats. The muscularis propria is thin. The tone of the muscle is only 30% and peristalsis and transit time are less than in conventional rats. The blood flow to the liver by the hepatic artery and portal vein is only 50% of that in the conventional rat.
Complete reduction of the enlarged cecum to the size in normal rats is only possible if the cecal contents or feces of normal rats are given to germfree rats. The concentration of bilirubin in the cecal content is enhanced whereas urobilin is absent from the urine of the germfree rats. The cecal content of germfree animals is lethally toxic for other animals after intraperitoneal injection.
Bacteroides sp., Peptococcus sp. and Clostridium difficile caused partial reduction of cecal size in germfree rats whereas Bacteroides fragilis and Streptococcus of group K caused even more enlargement in germfree rats (Juhr, 1972).
Perfusion of the cecum in germfree rats showed sixfold increase of resorption for monosaccharides and amino-acids in comparison with the conventional rat. Intestinal flora has a stimulating effect on the motility of the intestinal tract and the absence of flora leads to cecomegaly in rats (Juhr, 1971).
We found after 4+2 cm jejunoileal bypass a relative cecal weight of 2.5% and after 10% jejunoileal bypass a relative weight of 2.1% . These figures are low if compared to those in the germfree rat. However, the Zucker rat is a fat rat so any relation to body weight is distorted.
Sachdev (1979) measured the change in length of the cecum and its circumference at midpoint 4 weeks and 1 year after 90% jejunoileal bypass and 90% resection in Sprague-Dawley rats. Bypass and resection resulted in almost identical increases in cecal length (60%) and circumference (80%) after 4 weeks in comparison with sham rats. After 1 year these increases were 80% and 100%,respectively.
After our 4+2 cm jejunoileal bypass we find an increase of 73% and after 10% jejunoileal bypass an increase of 70% of the cecal circumference. It should be mentioned that we measured circumference not in the same plane as Sachdev did. Our

results also show that it takes more than 2 weeks to develop cecomegaly.
The increase in cecal circumference of 70% after jejunoileal bypass is not yet in the range of the fivefold increase found in germfree rats.
This may suggest a step by step increase of the cecal circumference, probably depending on a step by step decrease of cecal flora or a change of cecal flora.
Cecomegaly in rats may be important to investigate since after jejunoileal bypass in man sometimes a complication occurs, which is characterized by an atonic and largely distended colon. This phenomenon is called megacolon.

8.7 Summary

Jejunoileal bypass causes cecomegaly in Zucker rats.
However, cecomegaly in Zucker rats is not as prominent as it is known to exist in germfree rats. We cannot demonstrate any change of thickness of the cecal wall. This is in contrast to the reported decrease of thickness of all layers in germfree rats. Quantitative bacterial counts and anaerobic cultures show too much divergence to point to anaerobe bacteria as a causative factor in cecomegaly after jejunoileal bypass.
Cecomegaly may be seen as another mechanism of adaptation to reinforce absorption of monosaccharides and amino-acids.
Cecomegaly is probably accounted for by decrease and/or change of cecal flora.

MORBIDITY AND MORTALITY

9.1 Introduction

Grosfeld (1976) found in 15 Zucker rats after a jejunoileal bypass, which is comparable with our 10% jejunoileal bypass, a 20% anastomotic leak rate and a 33% mortality rate in a period of 4 months. He does not mention any other complications.
In view of these findings we recorded mortality and its causes, the condition of the hair of the animals and the presence of incisional hernia. Also, an unexpected complication occurred some weeks after operation: a perianal ulcer, which disappeared spontaneously in the majority of the cases, but in others resulted in death or in such a bad general condition that we were obliged to kill the rat.

9.2 Incisional hernia

Table 9.1 shows the number of rats with an incisional hernia in each experimental group 16 weeks after operation.

incisional hernia	*sham*	*4+2 cm*	*10%*	*p.c.s.*
absent	*5 (50%)*	*6 (30%)*	*10 (43%)*	*9 (90%)*
present	*5 (50%)*	*14 (70%)*	*13 (57%)*	*1 (10%)*
N	*10*	*20*	*23*	*10*

Table 9.1 Number of rats with incisional hernia 16 weeks after operation. N is number of rats.

It is clear that incisional hernia is predominantly seen after 4+2 cm jejunoileal bypass, viz. 70%.
This is probably caused by the loss of fat tissue and a less favourable nutritional condition. An additional cause might be provided by a lock-stitch suture being used for peritoneum and fascia, and including a mass of fat tissue in this fatty rat. The frequency of incisional hernia is significantly lower in the p.c. shunt group compared with the sham, 4+2 cm and 10% jejunoileal bypass groups ($p = 0.02$, chi-square test).
In man incisional hernia occurs in approximately 10% of the patients with a jejunoileal bypass (Butler, 1980).

9.3 Loss of hair

Loss of hair and a bad condition of the pelt may be considered symptoms of malnutrition and vitamin depletion.
Table 9.2 shows the frequency of this phenomenon in the 4 experimental groups 16 weeks after operation.

loss of hair	*sham*	*4+2 cm*	*10%*	*p.c.s.*
absent	*10*	*2 (10%)*	*10 (43%)*	*9*
present	*0*	*18 (90%)*	*13 (57%)*	*1*
N	*10*	*20*	*23*	*10*

Table 9.2 Number of rats showing loss of hair 16 weeks after operation in 4 experimental groups. N is number of rats.

Table 9.2 shows that loss of hair is essentially restricted to the two jejunoileal bypass groups. The difference from the sham group and the p.c. shunt group is significant ($p < 0.001$, chi-square test).
Furthermore, the occurrence of loss of hair is significantly greater after a 4+2 cm jejunoileal bypass than after a 10% jejunoileal bypass ($p = 0.04$, two-sided test of Hemelrijk).

9.4 Perianal ulcer

Almost all rats with a 4+2 cm jejunoileal bypass and a 10% jejunoileal bypass suffered from diarrhea during the first few weeks and some rats suffered from persistent diarrhea. As early as 3 days after operation some rats started to develop a perianal ulcer of varying size. Some rats developed a perianal ulcer after a few weeks. The course of this ulcer varied between spontaneous disappearance and deterioration by its invading into the perirectal fat, into the bladder area and even into the retroperitoneal space. Abscesses were found around the kidneys, in the liver and in the peritoneal cavity. Some rats had to be killed because of sepsis.
This complication has not been observed in either the sham group or in the p.c.shunt group.
Table 9.3 shows occurrence and the course of the perianal ulcer in the rats with a 4+2 cm and a 10% jejunoileal bypass.

perianal ulcer	4+2 cm and 10% jejunoileal bypass	
absent	19	(31%)
temporary	24	(39%)
cause of death	18	(30%)
N	61	

Table 9.3 Number of rats with a 4+2 cm and a 10% jejunoileal bypass showing no perianal ulcer, a temporary perianal ulcer or a perianal ulcer resulting in death. N is number of rats.

Since 30% of the rats with a bypass died or had to be killed because of perianal ulceration, this complication is very serious.
We could not demonstrate any relation between shunt length and mortality because of perianal ulcer (Spearman correlation).

9.5 Mortality

Apart from septic death due to perianal ulcer anastomotic leak was also a cause of death.
Rats with an anastomotic leak died on the second or third day after operation.
Table 9.4 shows the distribution of rats over the 4 experimental groups and the causes of death.

cause of death	sham	4+2 cm	10%	p.c.s.
anastomotic leak	0	4 (9%)	5 (13%)	0
perianal ulcer	0	9 (20%)	9 (23%)	0
other causes	5 (33%)	12 (27%)	2 (5%)	6 (37%)
killed after 16 weeks	10 (67%)	20 (44%)	23 (59%)	10 (63%)
N	15 (100%)	45 (100%)	39 (100%)	16 (100%)

Table 9.4 Cause of death in 115 fat Zucker rats distributed over 4 experimental groups. N is total number of rats in each group.

Anastomotic leak is almost equally present after 4+2 cm and 10% jejunoileal bypass, whereas the jejunal and ileal anastomoses after biopsies in the sham group and portacaval shunt

group never leak.
Altogether 9 rats died of anastomotic dehiscence. This amounts to 10.7% of all bypassed rats (84 rats) or 7.8% of all 115 rats in this table.
Not included in these 115 rats are those rats killed after 1 week and 2 weeks (N = 12) and those rats that remained in a metabolic cage (N = 10). Amongst them no leak occurred.
Including these additional 22 rats the leak rate is 6.6% of all operated rats (N = 137) and 8.7% of all bypassed rats. Our 8.7% anastomotic leak rate is considerably better than the 20% reported by Grosfeld (1976). This improvement is probably accounted for by the use of an operating microscope.
We can concur with Grosfeld's statement that the Zucker rat is a fragile rat since the overall mortality is 38% (52 out of 137 rats).
Altogether 25 rats died of other causes. Of these rats 3 died on account of pancreatitis, 3 died on account of instrumental problems at construction of the portacaval shunt, 1 died because of an embolus in the caval vein and 18 (= 13%) died because of anesthetic problems.
Liver failure has not been seen as a cause of death.

9.6 Conclusion

The Zucker rat is a delicate experimental animal.
The main problem is formed by anesthesia. Incisional hernia is often seen. Loss of hair as expression of malnutrition occurs nearly always after a 4+2 cm jejunoileal bypass and in more than 50% of the rats with a 10% jejunoileal bypass.
An unexpected complication of jejunoileal bypass is the development of a perianal ulcer, which caused death in approximately 30% of the bypassed rats.
Anastomotic leak occurs in 7% of the rats after jejunoileal bypass whereas it has not been observed after sham operation or portacaval shunt where intestinal biopsies were taken.
The use of an operating microscope probably reduces the frequency of anastomotic leak.

PART 2 RETROSPECTIVE STUDY

1.1 Introduction

This part of the thesis deals with some effects, positive as well as negative, of jejunoileal bypass in patients. Regrettably, not all data of the various patients were available, as is often the case in retrospective studies.
Data have been obtained from the surgical and medical records of St.Franciscus Gasthuis, Rotterdam, and from the surgical records of the University Hospital of Nijmegen.
A limited number of questions asked by telephone yielded an impression of the attitude of the patients towards effects and adverse effects of the operation.
Condensed versions of the case histories of 21 patients will be presented.
Subsequently we will summarize the available data on weight, weight reduction being the ultimate purpose of the operation, on complications and on satisfaction of the patients.
The expression "morbid obesity" was coined by Payne and De Wind in 1963 (Van Itallie, 1980).
Obesity is defined as an increase in body weight beyond the limitation of skeletal and physical requirement, as the result of an excessive accumulation of fat in the body (Dorland's Medical Dictionary, 1974). Van Itallie categorizes individuals who are 100% or more overweight as being morbidly obese.
Overweight can be calculated from the Broca index which gives the appropriate weight.
The appropriate weight in kg is height in centimetres minus 100. If body weight is greater than the height in centimetres - 100 , one is "overweight" and in most instances "obese" (Bray, 1976).
We use an adapted formula of the Broca index, viz. one according to Lorenz:

$$I.W. = \text{Length} - 100 - \frac{\text{Length} - 150}{4}$$

in which the ideal weight is expressed in kilograms and the length of the body in centimetres.
Morbid obesity is the essential indication for a jejunoileal bypass. Apart from being morbidly obese the patient has to meet all of several criteria which have been developed over the years.
Those criteria are the following: A weight of 80% or more above the ideal weight. The obesity must have existed for at least five years and a conscientious effort of conservative treatment must have failed. The patient should be more than 18 and less than 50 years of age. All organic causes, such as insulinoma, thyroid deficiency and Cushing's syndrome, must be ruled out.
The patient must be free of serious psychiatric disease and alcoholism.
He must be highly motivated having been told about all the risks of the procedure and its possible side-effects.
He must agree to being available for close follow-up study and

repeated hospitalization.
He must refrain from alcohol.
The liver function tests should not show significant abnormalities.
Reinforcing indications include the presence of some complications of morbid obesity, such as hypertension, myocardial infarction, diabetes, elevated blood lipid levels, stasis ulcers, intertrigo, Pickwickian syndrome, osteoarthritis or fertility problems (Phillips,1978).
The operation technique that was used is that described by Payne (1973). It includes an end-to-side anastomosis of 14 inches of jejunum (35 cm) to 4 inches of the distal ileum (10 cm).
The small intestine was measured halfway between the mesenteric and antimesenteric border in the first 15 patients that were operated upon in Rotterdam whereas in the 6 patients operated upon in Nijmegen measurements were performed at the mesenteric border.
If gallstones were present cholecystectomy was performed while appendectomy was performed as a matter of routine.

1.2 Case histories of 21 patients

Patient 1, a woman 38 years of age, had been obese since her 27th year. Her maximal weight was 133 kg whereas her ideal weight at a height of 150 cm would be 50 kg. Thus her actual weight was 266% of her ideal weight. Panniculectomy and several attempts with diets failed to result in persistent weight reduction. She suffered from hypertension, gallstones with intermittently raised liver function tests, urinary tract infections, a slightly abnormal glucose tolerance test, gonarthrosis and arthralgia of hands and feet. She occasionally complained of angina pectoris and exertional dyspnea. After admission and a rigorous diet in 1970 she reached a weight of 103 kg , which means an overweight of 106%. Then a 14-4 inch Payne shunt and a cholecystectomy were performed. Wound infection, hemorrhoidectomy, pyelotomy for the removal of stones, pseudo-obstruction and intermittently-raised-liver-function tests followed.
Nine years after jejunoileal bypass her weight was 73 kg. However, intractable diarrhea, severe hypokalemia and hypocalcemia, intolerable flatulence and decreasing levels of albumin, enforced restoration of normal anatomy. Within 9 months her weight had increased to 108 kg and subsequently a gastric bypass was performed.

Patient 2, a plumber, 26 years of age, had a 14-4 inch Payne shunt in 1973. Panniculectomy had been performed twice and diets yielded no results either. His blood pressure was 250 mm Hg systolic and 180 mm Hg diastolic.
On account of a maximal weight of 184 kg, which means 288% of ideal weight at a height of 169 cm , and low back pain he was not able to perform his profession any more. After admission and a rigorous diet he reached a preoperative weight of 154 kg, an overweight of 141%. After a relatively uneventful postoperative period of 4 years he was lost for follow-up.

Once he had been readmitted on account of severe anal discomfort and flatulence. An incisional hernia was found to be present. Blood pressure was 100 mm Hg systolic and 70 mm Hg diastolic.
His latest recorded weight was 87 kg. Thus he had lost 67 kg after the operation and 97 kg in comparison to the maximal weight, but still showed an overweight of 36%.
His withdrawal from follow-up might indicate that the patient was satisfied with the result of the operation as he had often expressed before he was lost sight of.

Patient 3, a widow at the age of 59, had been adipose since her 44th year. She became depressive as a reaction to the loss of her husband and loneliness and she did not leave her house any more. With a height of 155.5 cm and a maximal weight of 150 kg she weighed 278% of her ideal weight. Diabetes mellitus had been present for years, so had hypertension and chronic bronchitis. After admission and diet she reached a preoperative weight of 108 kg which is 100% overweight. A 14-4 inch Payne shunt and appendectomy were performed in 1973. She had to be readmitted three times because of diarrhea, anal discomfort and liver failure. One year after operation these symptoms, added to hypalbuminemia and severe edema, enforced operative intervention. Her weight was 71 kg then, a reduction of 37 kg. The 14-4 inch shunt was changed into a 24-14 inch shunt. Three years later, in which period a gastrointestinal bleeding occurred whereas liver function restored completely, her weight had increased to 124 kg, an overweight of 130%. Thereafter she was lost for follow-up. Liverbiopsy at the last operation showed massive fatty infiltration, much round cell infiltration and fibrosis.

Patient 4, an Indonesian woman aged 38, had been obese since the birth of her last child 11 years before operation. She did not dare to leave her house on account of an inferiority complex. Her maximal weight was 152 kg, 258% of ideal weight at a height of 162 cm. Several diets and medical treatments failed. After admission and rigorous dieting her preoperative weight was 120 kg, being 103% overweight.
A 14-4 inch Payne shunt and appendectomy were performed in 1973. A wound infection complicated the operation. After 3 years her weight was 81 kg, which increased to 100 kg after 8 years and 9 months. So she still had an overweight of 69%. The last 2 years she could not work as a nurse on account of gonarthrosis.

Patient 5, a housewife, 30 years of age, showed beginnings of adiposity at the age of 14 and at 15 years of age her weight was 95 kg . Her maximal weight was 121 kg , 191% of her ideal weight, at a height of 168 cm. Medical treatment failed to reduce weight by more than 21 kg . After admission and diet she reached a preoperative weight of 100 kg which means 57% overweight and then had a 16-6 inch end-to-side jejunoileal bypass and an appendectomy in 1974. Twice she suffered periods of abdominal cramps, vomiting and slight diarrhea and a plain abdominal X-ray showed some fluid levels. Barium enema and

barium meal examination were normal. With conservative treatment the complaints disappeared until 1977. Then the complaints increased seriously.
At laparotomy intussusception of the proximal end of the bypassed jejunum was found whereas the length of the functional segment had increased to 21 inches of jejunum and 9 inches of ileum, an increase of 31% and 50% respectively. Intussusception had occurred despite fixation of the proximal jejunum to the mesentery near Treitz's ligament at construction of the bypass.
The proximal part of excluded jejunum was resected and after closure of the stump it was again fixed to the mesentery. Since her weight before laparotomy had been at a steady level of 84 kg, another 7 inches of the functional jejunum were resected leaving a shunt of 14 inches of jejunum and 9 inches of ileum. After 1 month her weight had dropped further to 81 kg and thereafter gradually increased to a steady level of 95 kg 5 years later. Abdominal cramps did not occur any more.
The patient was not satisfied with an overall loss of weight of 5 kg since her first operation and a loss of weight of 26 kg compared with her maximal weight..
She could still perform her cleaning job as she used to before operation. Each time when she is eating too much, diarrhea is a warning sign.

Patient 6, a woman of 28, developed her obesity in the course of 2 years. She gained 46 kg and complained of backache, exertional dyspnea and giving-way of the knees. A slight diabetes mellitus was present as well as rheumatic arthritis of her left hand. At a body height of 162 cm her ideal weight was 59 kg . Her maximal weight was 105 kg which is 178% of ideal weight.
After clinical slimming to 96 kg a 14-4 inch Payne shunt was constructed in 1975. Panniculectomy followed in 1976 and in the same year a ureter stone was conservatively treated .
In 1977 intestinal obstruction because of internal hernia of the excluded segment required laparotomy. Cramps, foul smelling flatus and diarrhea, occasionally with blood and mucus, and abdominal distension as symptoms of pseudo-obstruction or enteropathy were treated in 1979. Diarrhea persisted up to 8 times a day and in 1981 an anal fissure required anal dilatation.
The ultimate result after 7 years is a weight of 64 kg which satisfies the patient fully but the complications would dissuade her from jejunoileal bypass if she would have to decide again.

Patient 7, a woman, aged 28, weighed 59 kg when she was 17. It took her only one year to reach 99 kg . Her ideal weight at a height of 164 cm should be 60.5 kg . Her maximal weight was 117 kg which is 197% of ideal weight. Diets gave unsatisfactory results. Diabetes mellitus was treated and after a clinical slimming period in which hyperuricemia caused some arthralgia she reached a preoperative weight of 104 kg. A 14-4 inch Payne shunt and appendectomy were performed in January 1975. Gallstones were not palpable, a finding consistent with normal X-

rays of the gallbladder.
Diarrhea up to 5 times a day persisted with intermittent exacerbation complicated by cramps and fluid levels on the plain abdomen in August 1975, a picture consistent with pseudo-obstruction. Cholecystectomy for multiple small stones and cholesterolosis of the gallbladder was performed in October 1975.
Ureterolithiasis was found in November 1975, in 1976 and in 1979.
Complaints of arthritis, starting in 1976 in one finger, increased and a few years later all fingers, wrists, shoulders and knees caused intermittent problems.
Anal blood loss explained by colitis and proctitis at endoscopy twice caused readmission in 1979.
In 1980 she was treated for duodenal ulcer. Hemorrhoidectomy followed in 1981.
A weight of 66 kg 7 years after jejunoileal bypass is a satisfying result but the number of complications has been too high in the opinion of our patient. She is still doing her job as a cleaner.

Patient 8 , owner of a snackbar, could not resist his own products. At the age of 20 he weighed 100 kg. At a height of 176 cm his ideal weight should be 69.5 kg. His maximal weight was 172 kg, which is 247% of ideal weight. Abuse of alcohol had been stopped 1 year before operation. A Pickwick syndrome, chronic asthmatic bronchitis, heart decompensation, hypertension and, ultimately, myocardial infarction in 1974 were indications for a 14-4 inch Payne shunt in 1975 when he was 44 years of age. After rigorous clinical dieting his preoperative weight was 104 kg.
Postoperatively a mechanical ileus developed responding well to conservative treatment.
After 4 months he refused follow-up and in 1976 he was readmitted for angina pectoris. Liver function tests were abnormal. Again he refused further follow-up and was three times admitted in 1981 on account of collapse, cardial and respiratory insufficiency and alcohol abuse. Several rehabilitation courses and trials by social workers failed since this patient was socially fully uncontrollable.
His latest recorded weight was 101 kg, which still means an overweight of 45%.

Patient 9, a 42-year-old woman from Surinam, had been obese from early childhood. Several diets had had no results. At a height of 152 cm her ideal weight was 51.5 kg . Her maximal weight was 122 kg which is 237% of ideal weight. Screening because of abdominal pain showed gallstones without abnormal liver function tests. Clinical dieting resulted in a preoperative weight of 106 kg and a 14-4 inch Payne shunt, cholecystectomy and appendectomy were performed in 1975. The liver was enlarged. After some time diarrhea subsided and she even complained of obstipation resulting in an anal fissure in 1977.
In 1976 signs and symptoms of pseudo-obstruction occurred temporarily.
Liver function tests only showed intermittent increases of

alkaline phosphatase, 132 U/l in July 1975, 155 U/l in July 1976 and 125 U/l in January 1977 (normal value of alkaline phosphatase: 20-120 U/l).
In all postoperative checks hepatomegaly persisted and biopsies of the liver were performed at operation, in February 1976, and in January 1977.
In August 1977 her weight was 64.5 kg and she went to Surinam to visit her relatives. Acutely ill, she was readmitted in November 1977. Serious anemia, hypocalcemia, hypophosphatemia, hypalbuminemia and elevated liver function tests were found. Despite intravenous alimentation and restoration of intestinal continuity this patient died in hepatic coma, 2 years and 10 months after jejunoileal bypass. Alcohol abuse had not occurred.

Patient 10, a woman, 44 years of age, with beginnings of obesity on her seventeenth, showed serious hypertension, a systolic pressure of 210 mm Hg and a diastolic pressure of 130 mm Hg, myocardial damage and exertional dyspnea. Her body height was 170 cm and her ideal weight 65 kg . Her maximal weight reached 124.5 kg which is 192% of ideal weight. Clinical weight reduction resulted in a weight of 105 kg and in 1975 a 14-4 inch Payne shunt was constructed. Anal discomfort, especially itching, as well as anal fissure occurred in 1977 . In 1981 diarrhea had changed into obstipation. This patient showed a dermatological complication 6 months after her bypass . An erythematous rash appeared over both elbows and knees. Biopsy showed a diffuse inflammatory reaction of the skin with several eosinophils, some edema, macrophages and destruction of nuclei.
Histologically it was identified as a phlegmonous inflammation without a clear cause.She received suppletion of iron and vitamin B12 for a persistent anemia with a low level of serum iron and a borderline low level of vitamin B12 .
Her final weight after 6.5 years was 102 kg, still an overweight of 57% after a loss of only 3 kg after the operation and a loss of 22.5 kg compared with her maximal weight..

Patient 11, a woman aged 51, showed onset of obesity after giving birth to her first child at the age of 24.
Her height was 173 cm resulting in an ideal weight of 67 kg . Her maximal weight was 166 kg which is 248% of ideal weight. Several clinical courses of slimming only had temporary effect. A psychiatrist diagnosed hyperorexia nervosa. Her blood pressure was 160 mm Hg systolic and 100 mm Hg diastolic and she complained of angina pectoris, palpitations, exertional dyspnea, arthrosis of both knees and spondylolisthesis of the fourth lumbar vertebra.
After reaching a preoperative weight of 119 kg clinically, she received a 14-4 inch Payne shunt and an appendectomy in 1975. Cholecystectomy had been performed in 1952 already.
She complained of anal pain, since diarrhea up to 15 times daily was still present after 4 months.
A follow-up of 6 years and 9 months showed intermittent signs of pseudo-obstruction and anal discomfort, increased pain of both knees and still a considerable exertional dyspnea, which

is quite understandable as she still weighed 119 kg . Her lowest weight had been 105 kg .
She would never want a jejunoileal bypass again. Because of myocardial problems a gastric bypass was considered too risky.

Patient 12 is a woman, 35 years of age. After giving birth at her twenty-first year her weight increased by 40 kg. Her maximal weight was 112 kg, 193% of her ideal weight of 58 kg, at a height of 161 cm .
Her main problem was a minority complex and she did not dare to leave her house. Her blood pressure was 165 mm Hg systolic and 100 mm Hg diastolic. Some exertional dyspnea was also present.
After trying to lose weight for 5 years in vain she was admitted and reached a preoperative weight of 100 kg.
A 14-4 inch Payne shunt was constructed.
Initially she had diarrhea up to 10 times a day , which improved to 4 times a day after 6 years and 3 months. Consistently using a 1000 Cal. diet she feels very well and is quite satisfied with a weight of 82 kg, which is still an overweight of 41%. She sells flowers in her own shop as she already did one month after operation.

Patient 13 has been obese since her fourteenth year. Extensive medical examination reveals adiposity at a maximal weight of 140 kg, at a body height of 177.5 cm and without other problems except some palpitations. Her ideal weight is 70.6 kg, thus her maximal weight is 197% of ideal weight. To stress the seriousness of obesity it is worthwile mentioning the sudden death of an obese uncle at the age of 23 and an obese aunt at the age of 29.
Several medical attempts at losing weight failed. Preoperative admission results in a weight of 99 kg and she receives a 14-4 inch Payne shunt and an appendectomy in 1976, at the age of 28. Anal discomfort due to diarrhea results in hemorrhoids and an anal fissure requiring anal dilatation after 3 months. In 1977 panniculectomy is performed, after which she develops a deep-vein thrombosis in her left leg and a pulmonary embolism. Nephrolithiasis resolves spontaneously in 1978 but requires pyelotomy in 1979, while she had passed a kidney stone 14 days before our telephonic inquiry in 1982.
Despite anticoagulants her left leg again shows a deep-vein thrombosis in 1979.
In 1980, 4 years postoperatively, her liver function tests deteriorate seriously while she feels very tired. Her weight is 97 kg .
Liverbiopsy in 1976 shows no signs of steatosis and only slight periportal infiltration of lymphocytes. Liverbiopsy in 1980 shows slight steatosis, periportal infiltration of lymphocytes, slight proliferation of bile ducts, hyperplasia of Kupffer's cells including PAS-positive material, and some focal loss of parenchyma, indicating a diagnosis of slight reactive hepatitis.
Restoration of intestinal continuity follows and the liver function tests improve. One and a half year after restoration her weight is 112 kg and since she still feels very tired and

the liver function tests have not yet totally normalized, gastric bypass is not yet under consideration.

Patient 14 is a 36-year-old woman who had been obese since her birth. Her body height was 178 cm resulting in an ideal weight of 71 kg. Her maximal weight was 142.5 kg, 201% of ideal weight.
Chronic bronchitis and hypertension (180/135 mm Hg) as well as a painful knee, painful ankles and low back pain were present. Attempts at slimming failed.
At a preoperative weight of 100 kg after clinical dieting a 14-4 inch shunt and appendectomy were performed in 1976.
Three weeks and five weeks after operation ileus occurred responding well to conservative treatment.
Diarrhea up to 30 times daily was treated with Vivonex. In 1977 and 1980 urolithiasis caused trouble. In 1979 she gave birth to a pair of twins. In 1981 liver function tests deteriorated and restoration of the shunt was considered but not performed. The tests improved slightly. Her latest recorded weight was 82 kg 5 years and 5 months after operation, which still means an overweight of 15%. The patient is very much in doubt as to whether she would choose a bypass again. Painful knees and ankles are still present as before the operation.

Patient 15, a 21-year-old man, showed first signs of obesity at the age of 14.
His maximal weight was 116 kg which is 184% of his ideal weight of 62 kg, at a body height of 167 cm.
Apart from some precordial pain there were no somatic complaints. Several attempts at losing weight failed. The liver function tests appeared to be moderately abnormal but improved after admission and weight was reduced to 95 kg. A 14-4 inch Payne shunt was performed in 1976.
Minor liver function test abnormalities were seen twice in 1978. All major joints started to ache in 1981 while all laboratory examinations to explain his joint pains proved negative.
After operation he did not change his eating habits. This resulted in diarrhea up to 20 times daily. For this reason he had to stop working as a clerk. His weight after 5 years has become 86 kg, which still means an overweight of 37%. The answer to the question about having a shunt again was ambivalent.

Patient 16, a man of 32, had been obese since his 7th year. His maximal weight had been 142 kg which is 212% of his ideal weight of 67 kg. His height was 173 cm. Several attempts to lose weight had failed. His blood pressure was 155 mm Hg systolic and 105 mm Hg diastolic. He complained of headache and a disability to mount his crane so he lost his job. Medical examination revealed no abnormalities except a raised level of serum triglycerides of 3.3 mmol/l (normal value 0.8 - 2.0 mmol/l). Cholesterol was within the normal range.
His preoperative weight was 121.5 kg, which meant an overweight of 81%. In 1979 a 14-4 inch Payne shunt was followed by a wound abscess. In March 1980 he showed signs of bypass

enteritis and in November 1980 he complained of painful loins. Microscopic hematuria was found together with many Ca-oxalate crystals in the urinary sedimentation. An intravenous urogram gave a normal picture . In January 1981 he complained of arthritis of the left ankle, of both wrists and hands, which disappeared spontaneously after 1 week. Two months later arthritis occurred again, and in both hands, his right elbow as well as his left hip now. Metronidazole for 5 days was very effective.
After a follow-up period of 2.5 years the patient is quite satisfied with a weight of 75 kg (an overweight of 12%)and a full-time job. Blood pressure is 120 mm Hg systolic and 80 mm Hg diastolic.
Triglycerides are normalized.

Patient 17, a woman aged 24, has been obese since her birth. Her weight at birth was 6.5 kg. Her maximal weight was 152 kg which was her preoperative weight. This was 259% of her ideal weight of 58.6 kg, at a body height of 161.5 cm . Her main problem was sterility which oppressed her so much that she once tried suicide. Amenorrhea and an enhanced level of luteinizing hormone were consistent with polycystic ovaries. Blood pressure was 180 mm Hg systolic and 110 mm Hg diastolic. Exertional dyspnea, especially when riding her bike to her job, kept her away from her job.
After a 14-4 inch Payne shunt in 1980 her only complaints were meralgia paresthetica in her right upper leg and a temporary loss of hair. She gave birth 16 months after the bypass, and after a follow-up period of 2 years and 6 weeks she is again pregnant. Her weight is 99 kg and her blood pressure is 130 mm Hg systolic and 90 mm Hg diastolic. The patient is quite satisfied with the results of the bypass procedure.

Patient 18, a 36-year-old woman, obese since her 14th year, had tried many diets without result. At a body height of 171 cm her ideal weight was 66 kg. Her maximal and at the same time preoperative weight of 143.5 kg was 217% of this ideal weight. Her main complaints were exertional dyspnea and painful feet restricting her to immobility.
Blood pressure was elevated, 160 mm Hg systolic and 120 mm Hg diastolic. She used antiepileptics. In 1980 a 14-4 inch Payne shunt was performed as well as appendectomy. Diarrhea up to 33 times a day in the beginning, diminishing to a mean of 5 times a day after 2 years caused her anal discomfort and finally hemorrhoids.
She had a short period of loss of hair and at the end of 1981 panniculectomy with abdominal skin reduction was performed. After a follow-up of 2 years her weight has reached 92.5 kg which still is an overweight of 40%) and the blood pressure is 120 mm Hg systolic and 80 mm Hg diastolic. She is able to cover 150 kilometres on her bike now. The patient is content with her situation.

Patient 19 is a housewife aged 23. She has always been obese whereas a twin brother has always been lean. Her maximal and at the same time preoperative weight was 145.5 kg which is

215% of her ideal weight of 67.6 kg . Many attempts at reducing weight failed. Exertional dyspnea, palpitations, low back pain, painful feet and a sense of shame were reasons for her to ask for a bypass procedure. Systolic blood pressure was 170 mm Hg while diastolic pressure was 110 mm Hg. Pulmonary function tests showed hypoxia. Serum cholesterol was normal whereas serum triglycerides were elevated, consistent with a mild form of hyperlipidemia, type II A according to Fredrickson.

In 1980 a 14-4 inch Payne shunt and appendectomy were performed. A few days after operation she showed signs of neuralgia paresthetica in both upper legs. Diarrhea, in the beginning up to 17 times a day and causing anal discomfort, decreased to 5 times a day after 1 year and 9 months. Her weight was 82 kg (still an overweight of 21%), blood pressure 115 mm Hg systolic and 65 mm Hg diastolic, cholesterol below the normal level and triglycerides at a low-normal level.

She feels socially adapted now and dares to do her own shopping again. She is content and wouldn't mind being subjected to the procedure once more.

Patient 20 had become obese at the age of 8. With a body height of 175 cm her ideal weight was 69 kg. Her maximal and at the same time preoperative weight was 137 kg , 199% of ideal weight. In 1979 she had passed a urinary concrement. All slimming courses, with and without psychological guidance, failed. A sense of shame and difficulty in making social contacts were major problems. At preoperative screening, interpretation of the intravenous cholangiogram was difficult while among the liver function tests only LDH was elevated.

In 1981, aged 30, a 14-4 inch Payne shunt was performed. Gallstones were palpated but because of a transverse incision removal was not possible in a one-stage procedure. Postoperative suppletion of potassium chloride was required and liver function tests worsened temporarily. She showed periodical loss of hair, and diarrhea initially caused anal discomfort. After a short follow-up of 38 weeks her weight is 103 kg now.

Patient 21 , a bank employee, had been obese since her birth, weighed 80 kg at her seventeenth year and reached a maximal and at the same time preoperative weight of 185 kg , 289% of an ideal weight of 62 kg at a body height of 166 cm.

Social contacts were limited resulting in depressions and abuse of alcohol. Clinical courses to lose weight and refrain from alcohol were without result except for the fact that one year before operation abuse of alcohol had been stopped. Medical screening demonstrated gallstones and elevated LDH. Blood pressure and serum lipids were normal. Psychiatric screening yielded no contraindications for a bypass. In 1981, aged 23, she had a 14-4 inch Payne shunt and a cholecystectomy. Initially the liver function tests deteriorated but improved after half a year, except for LDH. Anal discomfort was present although the frequency of diarrhea was "only" up to 7 times daily. Temporary loss of hair occurred.

After a follow-up period of 32 weeks, which is too short to be conclusive, her weight has reached 144 kg, which means a loss of 41 kg.

2.1 Loss of weight

If one wants to evaluate postoperative loss of weight the follow-up period is of paramount importance. Quaade (1979) and Andersen, Juhl and Quaade (1980) conducted a comprehensive survey of all publications recorded in MEDLARS and Index Medicus for the years 1963 up to the first half of 1977. They include the loss of weight of 1711 patients, reported in 45 publications: 33 kg after 6 months and 46 kg after 1 year on the average . After 2 years the mean loss of weight is 52 kg and the patient remains at this level. Only 5 publications including 346 patients, report a 5-year follow-up period and show this sustained loss of weight of 52 kg.
In our 21 patients we have to draw a distinction between the first 15 patients from Rotterdam and the last 6 patients from Nijmegen for 2 reasons. The maximal follow-up for Nijmegen is presently only 2.5 years, for Rotterdam it is 9 years, while all patients from Rotterdam were preoperatively admitted to try and reach loss of weight on a low-caloric diet. This procedure has not been followed in Nijmegen.
Table 2.2.1 gives weight characteristics and follow-up periods for all 21 patients.
The sex ratio is 17 to 4 in favour of female patients. The mean age of the patients is 34 years, ranging from 21 to 59 years. Since criteria for operation have developed gradually over the years, the third patient, aged 59, would not be eligible for operation now.
The average patient can anticipate losing one-third of his body weight, although there are great variations in both directions. The surgeon may consider this loss of weight of 30% of preoperative weight as an unfavourable result but patients often consider it a very successful result (Phillips, 1978).
Since loss of weight expressed in percentage of preoperative weight does not give any information as to the overweight position of the patient and as the preoperative starting position of patients 1 to 16 and 16 to 21 is different on account of preoperative dieting in the first group, postoperative overweight in percentage of ideal weight is also given For instance, after a follow-up period of 9 years patient 1 showed a good result measured by weight reduction. Her weight had dropped to 73 kg.
Unfortunately continuity had to be restored and events after this operation are recorded between brackets in table 2.2.1. One year and 8 months after restoration her weight had increased again by 37 kg resulting in an overweight of 120% of ideal weight and thus changing the patient's assessment of the results from good to bad.
The same applies to patient 3. A lengthening of the shunt to

pat.	sex	age yrs	id.wght kg	max.wght kg	% id w	preop.weight kg	% id w	follow-up	reoperation	weight loss kg	% preop	overweight % id.wght	pat.satisfaction
1	f	38	50	133	266	103	206	9y (+1y+8m)	restoration	30 (+37)	29 (+36)	46 (+120)	good(bad)
2	m	26	64	184	288	154	241	4y		67	44	36	good
3	f	59	54	150	278	108	200	1y (+3y)	lengthening	37 (+53)	34 (+49)	31 (+130)	good(bad)
4	f	38	59	152	258	120	203	8y+9m		20	17	69	bad
5	f	30	63.5	121	191	100	157	2y (+5y)	shortening	19 (+14)	19 (+14)	28 (+50)	bad (bad)
6	f	28	59	105	178	96	163	7y+1m		32	33	8	good
7	f	28	60.5	117	193	104	172	7y+1m		38	37	9	good
8	m	44	69.5	172	247	104	150	6y		3	3	45	bad
9	f	42	51.5	122	237	106	201	2y+10m	restoration	41.5	39	18	good(died)
10	f	44	65	124.5	192	105	162	6y+7m		3	3	57	bad
11	f	51	67	166	248	119	178	6y+9m		0	0	78	bad
12	f	35	58	112	193	100	172	6y+3m		18	18	41	good
13	f	28	71	140	197	99	139	4y (+1.5y)	restoration	2 (+15)	2 (+15)	37 (+58)	bad (bad)
14	f	36	71	142.5	201	100	141	5y+5m		18	18	15	good
15	m	21	63	116	184	95	151	5y+3m		9	9	37	bad
16	m	32	67	142	212	121.5	181	2y+6m		46.5	38	12	good
17	f	24	58.5	152	259	152	259	2y+6w		53	35	69	good
18	f	36	66	143.5	217	143.5	217	2y		51	36	40	good
19	f	23	67.5	145.5	215	145.5	215	1y+9m		63.5	44	21	good
20	f	30	69	137	199	137	199	38 wks		34	25	51	too early
21	f	23	62	185	298	185	298	32 wks		41	22	132	too early

Table 2.2.1 Weight characteristics, follow-up period and attitude of the patient towards loss of weight. In those patients where a reoperation of the shunt was performed, the data between brackets refer to results after reoperation.

24 inches of jejunum and 14 inches of ileum does not result in any weight reduction, but results in increase of weight as is the total small intestine is functioning again.
Patient 5 demonstrates that a 16-6 inch shunt does not reduce weight sufficiently because of intestinal adaptation as re-laparotomy shows after 2 years. The shunt had increased to a 21-9 inch shunt and was then shortened again to a 14-9 inch shunt. Five years after this shortening she had gained an additional 14 kg, so still an overweight of 50%, which has to be regarded as a bad result.
Patient 9 required restoration of continuity due to severe liver failure. Loss of weight had actually been good but this patient died in hepatic coma after restoration.
Patient 13 only lost 2 kg in a period of 4 years and after restoration of continuity, due to liver failure, she gained 15 kg in 1.5 year, resulting in an overweight of 58% : all in all an unsatisfactory result.
Patients 4,8,10,11 and 15 also showed insufficient loss of weight. For patients 20 and 21 the follow-up period is too short for any conclusions to be drawn regarding loss of weight. However, the loss of weight so far is sufficient.
If we thus consider 19 patients it appears that 12 patients (= 63%) show sufficient loss of weight whereas 7 patients (= 37%) show insufficient loss of weight.

2.2 Complications and adverse effects

In table 2.2.2 complications and adverse effects of jejuno-ileal bypass are given for 21 patients.
When a complication occurred more than once, even in one patient, it is included in the table.
Anal discomfort as a result of diarrhea is present very often. Diarrhea is actually present in all patients and may be considered obligatory after jejunoileal bypass. By the end of one year it has subsided from up to 20 stools a day to 2 or 3 soft stools a day unless the patient is eating too much.
For hypokalemia, hypomagnesemia, hypophosphatemia hypocalcemia and vitamin deficiencies some substitution was given. Extensive screening of all vitamins has only been performed in the last 5 patients.
It is very difficult to compare our results in a relatively small number of patients with the average results of Phillips (1978) and Quaade (1979). Quaade studied selected reports containing more than 50 patients.
Also, a number of complications mentioned by Quaade is not present in our series, e.g. psychiatric complications and suicide.
On the other hand meralgia paresthetica, as we found in 2 patients, has not been mentioned before while bypass enteritis or bypass enteropathy or pseudo-obstruction is a relatively new entity and not yet present in the list of complications as given by Quaade.
Meralgia paresthetica is thought to be the result of the overstretching of the lateral femoral cutaneous nerve at the point where it passes under the inguinal ligament when the patient is lying on his back on the operating table.

complications	number of patients	% of total	Phillips %	Quaade %
anal discomfort	17	81		
anal fissure	4	19		
hemorrhoids	7	33		
hemorrhoidectomy/dilatation	3	14	12	14
severe diarrhea	9	43		15
pseudo-obstruction	12	57		
colitis/proctitis	1	5		
gastro intestinal bleeding	1	5		
peptic ulcer	1	5		2
severe flatulence	5	24		1
early postoperative obstruction	2	10		
incisional hernia	5	24		
internal hernia	1	5		
invagination	1	5		2
wound infection/seroma	8	38		19
gallstones	1	5		6
kidney stones/hematuria	11	52	7	8
pyelotomy	2	10		
intermit. impaired liver tests	14	67		
seriously impaired liver tests	5	24	5	3
arthralgia	7	33	8	8
intermittent loss of hair	5	24	4-33	
LED-like skin	1	5		4
meralgia paresthetica	2	10		
leg thrombosis	2	10		1
pulmonary embolus	1	5		1
thrombophlebitis	4	19		
varicose veins	3	14		
pneumonia	1	5		
hypocalcemia	2	10	15	14
hypokalemia	6	29	25	17
hypomagnesemia	7	33	10	14
hypophosphatemia	2	10		
anemia	1	5		
folic acid deficiency	1	5		
hypocarotenemia	3	'14		
vitamin B12 deficiency	5	24		
vitamin E deficiency	6	29		
reoperation:				
shunt shortening	1	5		4
shunt lengthening	1	5		5
shunt restoration	2	10		2
death	1	5		4

Table 2.2.2 Complications and adverse effects in 21 patients with a 14-4 inch jejunoileal bypass according to Payne and a comparison with data from Phillips (1978) and Quaade (1979).

Passaro and Drenick (1976) describe bypass enteritis in the postoperative period as characterized by increased frequency of diarrhea, diffuse abdominal tenderness and distention, flatulence and fever. Roentgenographic studies disclosed multiple distended loops in the bypassed bowel with few air fluid levels. Antibiotic therapy had good results, in particular metronidazole (Paerregaard, 1982).
We encountered this picture 12 times, though not always a complete one with fever, and sometimes occurring many years after the operation. Presumably, it is caused by overgrowth of enteric bacteria in the distal portion of the bypassed bowel.
The liver function test abnormalities and liver biopsies have been extensively dealt with in chapter 7.
In 3 patients liver failure led to reconstruction of normal anatomy and 1 of these patients died.
We have found a remarkably high percentage of kidney stones, mainly because two patients suffered from kidney stones three times and 1 patient twice. Oxalate is normally excreted in the stool as calcium oxalate. However, after jejunoileal bypass and subsequent fat malabsorption the intraluminal calcium is used for the formation of soaps from fatty acids. Consequently, there is insufficient calcium to combine with oxalate in the lumen of the gut. Sodium oxalate is absorbed in the colon and excreted by the kidneys. In the nephron calcium becomes available with subsequent formation of insoluble calcium oxalate crystals. This may lead to urinary tract calculi, calcium oxalate nephro-calcinosis and even renal failure.
We did not find any abnormalities in the urea and creatinine levels in the serum of our 21 patients.
Severe electrolyte imbalance forced us to restore normal anatomy in 2 patients. In one of these it went together with severe liver failure and this patient died in hepatic coma.
In the 6 last patients vitamin levels were regularly assayed. Vitamin E deficiency was always present while hypocarotenemia was present in 3 patients. Vitamin A and D levels in the serum were always normal. Why vitamin A and D levels are normal and vitamin E level is lowered, all three being fat soluble vitamins, remains unexplained.
If we consider the attitude of the patients regarding the results in terms of loss of weight and complications, omitting the deceased patient and the last two patients with a too short follow-up period, 2 patients are very positive, 4 patients are positive, 2 patients are positive with strong reservations due to complications and 10 patients are negative.
This leads to a lower success figure (44%) than the 66% mentioned by Scott (1977) in two hundred patients and the 53% reported by Ravitch (1979) in 45 patients.
In conclusion one may state that jejunoileal bypass represents a massive assault on physiology and a major challenge to the organism's adaptive mechanisms. Even if it is used for only those morbidly obese patients who fulfil strict criteria the high frequency of complications appears, in our opinion, inacceptable.
Therefore, gastric procedures have to be preferred although in this field controversy still exists about the question what procedure gives the best results and the least complications.

SUMMARY AND CONCLUSIONS

Chapter 1 deals with the development of jejunoileal bypasses as treatment of morbid obesity. Results of animal experiments and of several intestinal bypasses in man are reviewed.
A comparison between the procedures suggested by Payne and Scott (an end-to-side anastomosis between 35 cm of proximal jejunum and 10 cm of distal ileum versus an end-to-end anastomosis between 30 cm of jejunum and 15 cm of ileum) reveals no decisive advantage in either of the two in their effects with respect to loss of weight and their complications. The total length of functioning small bowel appears critical in determining the weight-losing effect of the operation.
The aim of our study was to find a suitable method and a suitable animal model to identify and possibly standardize the parameters which affect both rate and size of loss of weight and which cause some of the complications after jejunoileal bypass surgery.

Chapter 2 describes the choice of the animal model. Characteristics of the genetically obese Zucker rat, called "Fatty", are given.

In chapter 3 the results of a pilot study in Wistar rats are shown. Then the 4 operative procedures in the Zucker rat are described extensively: the sham operation, the 4+2 cm jejuno-ileal bypass, the 10% jejunoileal bypass and the portacaval shunt.

Chapter 4 evaluates the body length of the rats, the length of the small intestine, the length of the functioning small intestine after construction of the jejunoileal bypasses, body weight and the postoperative changes of these parameters.
A jejunoileal bypass leaving 4 cm of jejunum and 2 cm of ileum as functioning intestine results in a significant growth retardation in the rat.
A 10% jejunoileal bypass and a portacaval shunt have the same effect though to a lesser degree.
The mean length of the small intestine of male fatty Zucker rats, calculated as the average of two measurements along the mesenteric border, is significantly greater than that of female fatty Zucker rats. Also, male fatty rats have a longer small intestine than their lean littermates.
The mean length of the functional small intestine in Zucker rats with a 4+2 cm jejunoileal bypass is 7% of the length of the small intestine.
The length of the functional small intestine increases significantly 6 weeks after a 4+2 cm or a 10% jejunoileal bypass. The relative increase appears to be more pronounced in the ileal part than in the jejunal part of the functional bypass. Examination of the 4+2 cm group indicates that this process only occurs from two weeks after operation.

In a period of 16 weeks sham rats gain weight in an almost linear way. The rats with a 4+2 cm jejunoileal bypass lose weight gradually and after 9 weeks their weight remains stable. The weight of the rats with a 10% jejunoileal bypass and the rats with a portacaval shunt hardly changes during the period of investigation.
The most decisive factor determining loss of weight after jejunoileal bypass is the length of the functioning segment in percentage of the total small intestinal length. A formula to predict loss of weight is given.

In chapter 5 blood samples have been assayed biochemically, preoperatively and 7 and 16 weeks postoperatively, in the 4 experimental groups.
Hemoglobin is lowered 7 weeks after a 4+2 cm jejunoileal bypass but after 16 weeks there is no significant difference with preoperative values in any of the groups.
Bilirubin, G.P.T. (glutamate pyruvate transaminase) and A.P. (Alkaline Phosphatase) are chosen as parameters for liver degeneration. None of these parameters shows any consistent increase after operation indicating liver failure. In fact, average G.P.T. and A.P. activities measured 16 weeks after 4+2 cm jejunoileal bypass, 10% jejunoileal bypass or portacaval shunt, are all lower than activities measured preoperatively. Thus, our data suggest that no liver damage occurs within the first 16 weeks after a jejunoileal bypass or a portacaval shunt in the fat Zucker rat.
Both jejunoileal bypass and portacaval shunt strongly affect the level of triglycerides in serum. Sixteen weeks after a 4+2 cm jejunoileal bypass or a 10% jejunoileal bypass a significant reduction in triglycerides is found. It appears that there exist pronounced differences in serum triglycerides between male and female Zucker rats.
After 16 weeks a 4+2 cm jejunoileal bypass lowers significantly the level of cholesterol in the serum in comparison with its preoperative value. However, this decrease is not significant in comparison with the change of the level of cholesterol in sham rats 16 weeks after operation.
A portacaval shunt lowers serum cholesterol significantly.

Chapter 6 reports the morphological changes in the small intestine after a jejunoileal bypass, a portacaval shunt or a sham operation.
Intestinal adaptation occurs after extensive resections and after bypass procedures of the small intestine.
In the fat Zucker rat adaptation of the intestine after jejunoileal bypass has not been demonstrated before.
Adaptation of the small intestine appears to consist of two separate and subsequent mechanisms: firstly, an increase of thickness of the entire intestinal wall, mostly by increase of villous height and muscularis propria, and secondly, an increase of intestinal length and circumference.
This adaptation of the functioning intestine after jejunoileal bypass is responsible for the slow gain of weight after an initial loss of weight and is one of the factors contributing to the ultimate result of loss of weight by jejunoileal

bypass.
After a jejunoileal bypass it takes one to two weeks before atrophy of the excluded intestine starts to become visible and after 16 weeks atrophy is clearly visible.
The thickness of all intestinal layers of the excluded jejunum and ileum hardly changes 16 weeks after operation except for some increase of muscularis propria, especially in the excluded distal ileum.
Macroscopic reflux of chyme from the colon ascendens into the excluded distal ileum finds only minor expression in the microscopic measurements of the distal ileum.
In the portacaval shunt rats a striking increase of muscularis propria is found in both the jejunum and the ileum 16 weeks after construction of the shunt.

Chapter 7 discusses the hepatic histology of the fat Zucker rat. The fat Zucker rat is characterized by steatosis of the liver with a preponderance in the area between the periportal and pericentral area: the mid-zonal area.
A 4+2 cm jejunoileal bypass shows significant reduction in steatosis of the liver in the pericentral zone, the periportal zone and the zone between the pericentral and periportal area, 16 weeks after operation.
A 10% jejunoileal bypass has the same effect but only in the mid-zonal and pericentral areas whereas after a portacaval shunt significant reduction of steatosis occurs in the mid-zonal area.
The liver of rats with a portacaval shunt shows remarkable increase of siderosis.
Degeneration of the liver, characterized by the presence of Councilman bodies, inflammation of the portal triads, Mallory bodies and degeneration of groups of liver cells is one of the most feared complications after jejunoileal bypass. This degeneration of the liver cannot be demonstrated in our rats.
Several theories to explain the cause of liver insufficiency are discussed.
Analogous to the reduction of blood flow to the liver in a portacaval shunt, reduction of blood flow to the liver in a jejunoileal bypass is postulated as one of the factors contributing to liver disease after jejunoileal bypass.

In chapter 8 a phenomenon is discussed observed in experiments with germfree rats: cecomegaly, an enormous distension of the cecum.
A short review of cecomegaly in literature is given.
Cecomegaly is probably accounted for by decrease and/or change of cecal flora.
Jejunoileal bypass causes cecomegaly in Zucker rats.
Quantitative bacterial counts and anaerobic cultures of homogenized ceca show too much divergence to point to anaerobe bacteria as a causative factor in cecomegaly after jejunoileal bypass.
In contrast to the reported decrease of thickness of all layers of the cecal wall in germfree rats, we cannot demonstrate any change of thickness of the cecal wall layers after jejunoileal bypass in the fat Zucker rat.

Chapter 9 reviews morbidity and mortality in our experiment. The fat Zucker rat is more fragile than the conventional laboratory rat. Anaesthesia is one of the problems. Some complications after jejunoileal bypass are discussed such as the development of a perianal ulcer.
The use of microsurgical technique probably reduces the high frequency of anastomotic leak in the fat Zucker rat.

Part two of this thesis deals with a retrospective study of 21 patients with morbid obesity. Patients who are 100% or more overweight are considered morbidly obese. These 21 patients have been treated by a jejunoileal bypass according to Payne.

Results of loss of weight are given in chapter two, with particular attention to the complications after jejunoileal bypass.
The conclusion of both the results reported in literature and the present retrospective study is evident:
Jejunoileal bypass is not the first choice of surgical treatment for morbid obesity any more. The recently developed gastric procedures which restrict the gastric volume are to be preferred.

Samenvatting en conclusies

Hoofdstuk 1 vermeldt de ontwikkeling van de kortsluitingsoperaties van het jejunum en het ileum ter behandeling van extreme vetzucht. Resultaten van dierexperimenteel onderzoek en van diverse vormen van kortsluitingen van de dunne darm bij de mens worden besproken. De procedure volgens Payne, in wezen bestaande uit een end-to-side anastomose tussen 35 cm van het proximale jejunum en 10 cm van het distale ileum, bleek in gewichtsverlies en het optreden van complicaties bij patiënten hetzelfde resultaat op te leveren als de procedure volgens Scott. Deze procedure bestaat uit een end-to-end anastomose tussen 30 cm van het proximale jejunum en 15 cm van het distale ileum met drainage van de uitgeschakelde dunne darm in het colon.
De lengte van het stuk functionerende dunne darm is essentieel voor de effectiviteit van de operatie.
Het doel van onze studie was een geschikt dierexperimenteel model te vinden en vervolgens verscheidene parameters te onderzoeken die bepalend zouden kunnen zijn voor de mate en de snelheid van het gewichtsverlies en de mogelijke complicaties na een jejunoileale kortsluitingsprocedure.

In hoofdstuk 2 wordt de keuze van het proefdier beschreven. De eigenschappen van de genetisch vette Zucker rat, bijgenaamd "dikzak" ("Fatty") , worden nader toegelicht.

Hoofdstuk 3 geeft de resultaten van een voorstudie met Wistar ratten. Vervolgens worden in extenso de vier operatieprocedures bij de Zucker rat besproken: ratten met een schijnoperatie, ratten met een 4+2 cm jejunoileale kortsluitingsprocedure, ratten met een 10% jejunoileale kortsluitingsprocedure en ratten met een portocavale shunt.

Hoofdstuk 4 behandelt de lichaamslengte van de ratten, de lengte van de dunne darm, de lengte van het nog functionerende stuk dunne darm na aanleggen van de kortsluiting, het lichaamsgewicht en de postoperatieve veranderingen in deze parameters.Een kortsluitingsprocedure waarbij nog 4 cm jejunum en 2 cm ileum van de rat functioneren levert evenals een jejunoileale kortsluitingsprocedure van 10% of een portocavale shunt, zij het in mindere mate, een duidelijke groeivertraging van de rat op.
De dunne darm van vette mannelijke Zucker ratten, berekend als het gemiddelde van 2 metingen langs de mesenteriale zijde van de darm, is significant langer dan die van vette vrouwelijke Zucker ratten en eveneens significant langer dan die van magere mannelijke Zucker ratten.
De gemiddelde lengte van het functionele stuk dunne darm bij de Zucker ratten met een 4+2 cm kortsluitingsprocedure is 7% van de totale dunne darm lengte. De lengte van dit functionele stuk dunne darm blijkt 16 weken na een 4+2 cm of 10% jejunoileale kortsluitingsprocedure te zijn toegenomen. De toename van de lengte van het functionerende stuk dunne darm vindt relatief meer plaats in het ileum dan in het jejunum.

Deze toename treedt pas op vanaf 2 weken na de operatie. Curves van het lichaamsgewicht over een periode van 16 weken laten zien dat de ratten uit de controle groep vrijwel lineair blijven groeien, terwijl de ratten met een 4+2 cm kortsluitingsprocedure gedurende 9 weken gewicht verliezen en vervolgens stabiel blijven. De ratten met een 10% kortsluitingsprocedure evenals de ratten met een portocavale shunt blijven vrijwel op het preoperatieve gewicht.
De parameter die de grootste bijdrage levert tot het gewichtsverlies na een kortsluitingsprocedure van de dunne darm is de lengte van het functionerende stuk dunne darm , uitgedrukt als percentage van de lengte van de gehele dunne darm. Om het gewichtsverlies te voorspellen wordt een formule opgesteld.

In hoofdstuk 5 worden verscheidene biochemische serumbepalingen besproken bij de 4 experimentele groepen en wel preoperatief, 7 en 16 weken postoperatief.
Het hemoglobine gehalte blijkt 7 weken na een 4+2 cm kortsluitingsprocedure gedaald te zijn. Na 16 weken echter is er geen significant verschil met de preoperatieve waarden in alle groepen.
Bilirubine, S.G.P.T. 8 serum glutamaat pyruvaat transaminase) en A.F. (alkalische fosfatase) zijn bepaald als parameters voor de leverfunktie. Geen van deze parameters laat een consequente stijging zien na de operatie ten teken van leverfunktiestoornissen. De gemiddelde waarden van S.G.P.T. en van A.F. zijn 16 weken na een 4+2 cm, een 10% kortsluitingsprocedure of een portocavale shunt in feite lager dan preoperatief. Dit wekt de suggestie dat binnen de eerste 16 weken na een jejunoileale kortsluitingsprocedure of een portocavale shunt bij de vette Zucker rat geen leverbeschadiging optreedt.
Zowel de jejunoileale kortsluitingsprocedures als de portocavale shunt hebben een duidelijke invloed op het triglyceride gehalte in het serum. Zestien weken na een 4+2 cm of een 10% kortsluitingsprocedure wordt een significante daling van de triglyceriden gevonden. Er blijken uitgesproken verschillen te bestaan in de triglyceriden concentraties van mannelijke en vrouwelijke Zucker ratten.
Na 16 weken doet een 4+2 cm jejunoileale kortsluiting het cholesterol gehalte in het serum significant dalen vergeleken met de preoperatieve waarde, echter deze daling is niet significant vergeleken met de verandering in de de waarde van controle ratten 16 weken na de operatie.
Een portocavale shunt verlaagt het serum cholesterol wel significant.

Hoofdstuk 6 behelst de morphologische veranderingen van de dunne darm na jejunoileale kortsluiting, portocavale shunt of een schijnoperatie.
Aanpassing van de dunne darm treedt op na uitgebreide resecties of kortsluitingsoperaties van de dunne darm. Tot nu toe is adaptatie van de dunne darm bij de vette Zucker rat nog niet aangetoond. Adaptatie van de dunne darm blijkt te bestaan uit twee verschillende en na elkaar optredende mechanismen: aanvankelijk een toename van de dikte van de gehele wand van

de dunne darm, vooral bepaald door toename van de villus hoogte en de dikte van de muscularis propria, en vervolgens een toename van de lengte en de omtrek van de dunne darm. Deze adaptatie van het functionerende stuk dunne darm na jejuno-ileale kortsluiting is verantwoordelijk voor de langzame gewichtstoename na een aanvankelijk gewichtsverlies en is een van de factoren die bijdragen tot het uiteindelijke resultaat wat betreft gewichtsverlies.
Het uitgeschakelde stuk dunne darm begint na 1 tot 2 weken atrofisch te worden hetgeen na 16 weken zeer duidelijk is. Het uitgeschakelde stuk jejunum en ileum laat op microscopisch niveau na 16 weken nauwelijks verandering zien behoudens enige toename van de muscularis propria, vooral in het distale ileum. Het al dan niet aanwezig zijn van reflux van darminhoud van het colon ascendens naar het uitgeschakelde stuk distale ileum blijkt nauwelijks in relatie te staan met de microscopische parameters van de darmwand.
Bij de ratten met een portocavale shunt valt op dat de muscularis propria is toegenomen in dikte, zowel in het jejunum als in het ileum, 16 weken na aanleg van de shunt.

De histologie van de lever van de vette Zucker rat komt aan de orde in hoofdstuk 7. De lever van de vette Zucker rat wordt gekenmerkt door steatose, vooral in het intermediaire gebied, hetwelk gelegen is tussen het periportale en pericentrale gebied. Een 4+2 cm jejunoileale kortsluiting laat na 16 weken een significante vermindering van de steatose zien, zowel pericentraal, intermediair als periportaal.
Een 10% jejunoileale kortsluiting heeft hetzelfde effect echter allen intermediair en pericentraal, terwijl na een portocavale shunt alleen in het intermediaire gebied een significante vermindering van de steatose optreedt. Bij de portocavale shunt wordt een opmerkelijke toename van siderosis van de lever gezien.
Levercel verval, gekenmerkt door de aanwezigheid van Councilman bodies, ontsteking van de portale driehoekjes, Mallory bodies en groepjes gedegenereerde levercellen, is een van de meest gevreesde complicaties na jejunoileale kortsluiting. In geen van de ratten is dit levercel verval aangetoond. Verscheidene theorieën welke de oorzaak van de leverinsufficiëntie proberen aan te geven worden besproken.
In analogie aan de portocavale shunt wordt gesteld dat de verminderde toevoer van bloed naar de lever via het vena portae systeem een van de mogelijke factoren is die bijdraagt tot de genoemde leverinsufficiëntie na een jejunoileale kortsluitingsprocedure.

In hoofdstuk 8 wordt een fenomeen besproken dat bekend is uit dierexperimenten met kiemvrije ratten: coecomegalie d.w.z. een forse toename van de grootte van het coecum. In het kort wordt de literatuur over coecomegalie vermeldt. Coecomegalie zou waarschijnlijk het gevolg zijn van vermindering en/of een verandering van de bacteriële flora van het coecum.
Jejunoileale kortsluiting veroorzaakt coecomegalie bij de vette Zucker rat.
Bacterietellingen en anaerobe kweken van gehomogeniseerde

coeca laten echter te veel spreiding zien om aan te tonen dat anaerobe bacteriën coecomegalie veroorzaken na jejunoileale kortsluiting. In tegenstelling tot gegevens uit de literatuur over kiemvrije ratten blijkt uit onze metingen dat de dikte van alle lagen van de wand van het coecum niet afneemt na jejunoileale kortsluiting bij de vette Zucker rat.

Hoofdstuk 9 geeft een overzicht van de morbiditeit en de mortaliteit in het experiment. De vette Zucker rat is minder sterk dan de conventionele laboratorium rat. De anaesthesie levert meer problemen op. Enkele complicaties na jejunoileale kortsluiting worden besproken zoals het optreden van een perianaal ulcus.
Door gebruik te maken van microchirurgische techniek wordt de hoge frequentie van naadlekkage bij de vette Zucker rat waarschijnlijk gereduceerd.

Deel twee van dit proefschrift houdt zich bezig met een retrospectieve studie van 21 patiënten met morbide obesitas, d.w.z. patiënten met meer dan 100% overgewicht. Deze patiënten zijn behandeld met een jejunoileale kortsluitingsprocedure volgens Payne.
In hoofdstuk 1 worden de criteria genoemd waaraan de patiënten met morbide obesitas moeten voldoen om in aanmerking te komen voor een jejunoileale kortsluitingsprocedure. Dan volgt in het kort de geschiedenis van elk van deze 21 patiënten.

Hoofdstuk 2 geeft een overzicht over de resultaten wat betreft gewichtsverlies en legt vooral de nadruk op de complicaties.
De conclusie die uit de literatuurgegevens en deze retrospectieve studie getrokken moet worden is duidelijk.
De jejunoileale kortsluitingsprocedure is niet meer de operatieve behandeling van eerste keuze bij patiënten met morbide adipositas nu diverse procedures die de maag verkleinen ontwikkeld zijn.

ACKERMAN, N.B. (1982): Changes in serum cholesterol and triglyceride levels after jejunoileal and gastric bypasses in morbidly obese patients.
Surg. Gynecol. Obstet. 154: 1-7.

AMES, F.C., COPELAND, E.M., LEEB, D.C., MOORE, D.L., DUDRICK, S.J. (1976): Liver dysfunction following small-bowel bypass for obesity. Nonoperative treatment of fatty metamorphosis with parenteral hyperalimentation.
J. Am. Med. Assoc. 235: 1249 - 1252.

ANDERSEN, T. , JUHL, E. , QUAADE, F. (1980): Jejunoileal bypass for obesity. What can we learn from a literature study.
Am. J. Clin. Nutr. 33 , 440 - 445.

ANSON, B.J. , (1971): In: Surgical Anatomy. Anson, B.J., McVay, C.B. , p. 639 Saunders, Philadelphia, U.S.A.

ARMELLINI, F., BOSELLO, O., BAGGIO, E., BELLIGOLI, A.M., FACCIOLI, G., OTTOLENGHI, A. (1976): Il by-pass digiuno-ileale nel tratttamento dell'obesita 'sperimentale del ratto.
Chir. Patol. Sper. 24: 111 - 118.

AYERS, W.M. (1958): Changing attitudes toward overweight and reducing.
J. Am. Dietetic Assoc. 34: 23 - 29.

BACH, A., BAUER, M., SCHIRARDIN, H., (1977): Data on lipid metabolism in the genetically obese Zucker rat.
Life Sci. 20: 541 - 550.

BACKMAN, L., HALLBERG, D., (1974): Small-intestinal length.
Acta Chir. Scand. 140: 57 - 63.

BACKMAN, L., (1975): The rate of weight loss after intestinal bypass operations for obesity.
Acta. Chir. Scand. 141: 424 - 430.

BACKMAN, L., HALLBERG, D. (1975): Some somatic complications after small intestinal bypass operations for obesity. Possible factors of significance in the incidence.
Acta Chir. Scand. 141: 790 - 800.

BAGGIO, E., BOSELLO, O., MAGAGNOTTO, S., ARMELLINI, F., FACCIOLI, G., OTTOLENGHI, A. (1976): Il by-pass digiuno-ileale nel trattamento dell'obesita 'sperimentale del ratto.
Chir. Pat. Sper. 24: 105 - 110.

BARRY, W.S., BRAY, G.A., (1969): Plasma triglycerides in genetically obese rats.
Metabolism, 18: 833 - 839.

BARRY, R.E., BARISCH, J., BRAY, G.A., SPERLING, M.A., MORIN, R.J., BENFIELD, J., (1977): Intestinal adaptation after jejunoileal bypass in man.
Am. J. Clin. Nutr. 30: 32 - 42.

BECKER, E.E., GRINKER, J.A., (1977): Meal patterns in the genetically obese Zucker rat.
Physiol. Behav. 18: 685 - 692.

BENFIELD, J.R., GREENWAY, F.L., BRAY, G.A., BARRY, R.E., LECHAGO, J., MENA, I., (1976): Experience with jejuno-ileal bypass for obesity.
Surg. Gynec. Obstet. 143: 401 - 410.

BESSEY-DE VRIES, (1956): In: Klinische diagnostiek. E. Gorter, W.C. de Graaff , 7e druk, deel I , p 322 , Stenfert Kroese n.v. , Leiden, The Netherlands.

BOCHKOV, N.P. (1959): Morphological changes in the jejunum and ileum of rats after wide resection of the small intestine.
Bull. Exp. Biol. Med. 47: 339.

BOCHKOV, N.P. (1958): Morphological and physiological changes in the small intestine of the dog after its partial resection.
Bull. Exp. Biol. Med. 46: 1261 - 1265.

BOCKUS, H.L., (1964): Gastroenterology, 2nd ed. vol. II, p 10 - 15 .
W.B. Saunders, Philadelphia, London.

BOND, J.H., PRENTISS, R.A., LEVITT, M.D., SCHOENBORN, K., (1979): The effects of feeding on blood flow to the stomach, small bowel, and colon of the conscious dog.
J. Lab. Clin. Med. 93: 594 - 599.

BONDAR, G.F., PISESKY, W. (1967): Complications of small intestinal short-circuiting for obesity.
Arch. Surg. 94: 707 - 716.

BRANCH, C.D., EBENSTEIN, R.S., BORGIA, J.F., HORVATH, S.M., PRESTON, F.W. (1980): Complications of jejunoileal bypass related to the excluded segment.
Surg. Gynec. Obstet. 150: 353 - 356.

BRAY, G.A., YORK, D.A. (1972): Studies on food intake of genetically obese rats.
Am. J. Physiol. 223: 176 - 179.

BRAY, G.A., YORK, D.A., SWERDLOFF, R.S. (1973): Genetic obesity in rats, 1. The effects of food restriction on body composition and hypothalamic function.
Metabolism, 22: 435 - 442.

BRAY, G.A., LUONG, D., YORK, D.A. (1974): Regulation of adipose tissue mass in genetically obese rodents, in: The regulation of the adipose tissue mass.
Eds. Vague,J., Boyer. p 112 - 121 Excerpta Medica Amsterdam.

BRAY, G.A. (1976): The Obese Patient. p.6.
W.B. Saunders Cy, Philadelphia, London, Toronto.

BRAY, G.A. (1977): The Zucker-fatty rat: a revieuw.
Fed. Proc. 36: 148 - 153.

BUCHWALD, H., VARCO, R.L. (1971): A bypass operation for obese, hyperlipidemic patients.
Surgery, 70: 62 - 70.

BUCHWALD, H., RUCKER, R.D., SCHWARTZ, M.Z., VARCO, R.L. (1981): Positive results of jejunoileal bypass surgery: emphasis on lipids with comparison to gastric bypass.
Intern. J. Obesity 5: 399 - 404.

BURNEY, D.P., BURNHAM, S.J., HOUGH, A.J., SCOTT, H.W. (1977): Experimental short gut: hepatic alterations after jejuno-ileal resection, bypass and vibramycin therapy.
Am. Surg. 43: 778 - 786.

BUTLER, C.M., PILKINGTON, T.R.E., GAZET, J-C. (1980): Complications of jejunoileal bypass surgery. In: Surgical management of obesity, p. 214. Maxwell, Gazet, Pilkington. Academic Press: London, Toronto, Sydney
Grune and Stratton: New York, San Francisco

COMAI, K., TRISCARI, J., SULLIVAN, A. (1978): Differences between lean and obese Zucker rats: the effect of poorly absorbed dietary lipid on energy intake and body weight gain.
J. Nutr. 108: 826 - 835.

DALY, J.M., CASTRO. G.A., AKHTAR, M. DUDRICK, S.J. (1977): Morphologic and biochemical intestinal changes after jejunoileal bypass.
Review of Surgery, Nov-Dec.: 428 - 431.

DANØ P., JARNUM, S., NIELSON, O.V. (1973): Intestinal shunt operation in obesity. A comparison of three types of operation.
Scand. J. Gastroenterol. 8: 457 - 464.

DEENSTRA (1952): in: Noyons no III, p 216 - 221, van Holkema en Warendorf, Amsterdam, The Netherlands.

DE MUTH, W.E., ROTTENSTEIN, H.S. (1964): Death associated with hypocalcemia after small bowel short circuiting.
New Eng. J. Med. 270: 1239.

DORLAND'S ILLUSTRATED MEDICAL DICTIONARY (1974), Twenty-fifth edition.
W.B. Saunders. Philadelphia, London, Toronto.

DOWLING, R.H., BOOTH, C.C. (1966): Functional compensation after small bowel resection in man; demonstration by direct measurement.
Lancet, 2: 146.

DRENICK, E.J., SIMMONS, F., MURPHY, J.F. (1970): Effect on hepatic morphology of treatment of obesity by fasting, reducing diets and small-bowel bypass.
New Engl. J. Med. 282: 829 - 834.

DUDRICK,S.J., DALY, J.M., CASTRO, G., AKHTAR, M. (1977): Gastrointestinal adaptation following small bowel bypass for obesity.
Ann. Surg. 185: 642 - 648.

FAIRCLOUGH, P.D., KUMAR, P.J., CLARK, M.L., AGGIS, A., RIMMER, D., PILKINGTON, T.R.E., GAZET, J-C. (1980): Intestinal Adaptation" in: Surgical management of obesity, p. 104 - 106 by Maxwell, J.D., Gazet, J-C., Pilkington T.R.E., Academic Press: London,Toronto, Sydney
Grune and Stratton: New York, San Francisco.

ELIAS, E., DOWLING, R.H. (1976): The mechanism for small bowel adaptation in lactating rats.
Clin. Sci. Mol. Med., 51: 427 - 433.

FENYØ G., BACKMAN, L., HALLBERG, D. (1976): Morphological changes of the small intestine following jejunoileal shunt in obese subjects.
Acta Chir. Scand. 142: 154 - 159.

FENYØ G., HALLBERG, D. (1976): Intestinal hypertrophy after small intestinal bypass in the rat.
Acta Chir. Scand. 142: 261 - 269.

FREDRICKSON, D.S., GOLDSTEIN, J.L., BROWN, M.S. (1978): The familial hyperlipoproteinemias, in Stanbury, J.B. , Wyn-

gaarden, J.B., Fredrickson, D.S. (eds): The metabolic Basis of Inherited Disease (ed. 4). New York, McGraw-Hill, p 604 - 655.
FRIEDMANN, H.I., CHANDLER, J.G., PECK, C.C., NEMETH, T.J., ODUM, S.K. (1978): Alterations in intestinal structure, fat absorption and body weight after intestinal bypass for morbid obesity.
Surg. Gynec. Obstet. 146: 757 - 767.
FRIEDMANN, H.I., VILLAR, H.V., NEMETH, T.J. (1981): The mucosal response in the excluded limb after jejunoileal bypass for morbid obesity.
Surg. Gynec. Obstet. 153: 346 - 350.
GARDNER, E. (1966): In: Anatomy.
Gardner, E., Gray, D.J., O'Rahilly, R., 2nd edition, p 498 Saunders, Philadelphia, U.S.A.
GASPAR, M.R., MOVIUS, H.J., ROSENTHAL, J.J., ANDERSON, D. (1976): Comparison of Payne and Scott operations for morbid obesity.
Ann. Surg. 184: 507 - 513.
GRANGER, D.N., RICHARDSON, P.D.I., KVIETYS, P.R., MORTILLARO, N.A. (1980): Intestinal blood flow.
Gastroenterology, 78: 837 - 863.
GRENIER, J.F., ELOY, M.R., JAECK, D., DAUCHEL, J. (1974): Court-circuit jéjunoileal. Adaptation fonctionelle et histologique de grèle en circuit et hors circuit.
Chirurgie, 100: 59 - 65
GRENIER,J.F., DAUCHEL, J., MARESCAUX, J., ELOY, M.R., SCHANG, J.C. (1977): Intestinal changes after jejunoileal shunt in obesity: a report of 2 cases.
Br. J. Surg. 64: 96 - 99.
GROSFELD, J.L., COONEY, D.R., CSICSKO, J.F., MADURA, J.A. Adverse effects of jejunoileal bypass on growth and development.
Surgery, 80, 2: 201 - 207.
GROSFELD, J.L., HARRIS, R.A., CSICSKO,J.F., COONEY, D.R., MADURA, J.A. (1977): Increased hepatic synthesis of cholesterol following jejunoileal bypass.
Surgery, 81: 701 - 107.
GUINNESS BOOK OF RECORDS, 1981
GUSTAFSSON, B. (1959): Germfree research at the institute of histology University Lund. In: Recent progress in microbiology. Oxford, p 320 - 326.
GUZMAN,I.J., VARCO, R.L., BUCHWALD, H. (1975): Factors determining weight loss after jejunoileal bypass for obesity.
J. Surg. Research 18, 399 - 403.
HALVERSON, J.D., WISE, L., WAZNA, M.F., BALLINGER, W.F. (1978): Jejunoileal bypass for morbid obesity. A critical appraisal.
Am. J. Med. 64: 461 - 475.
HALVERSON, J.D., SCHEFF, R.J., GENTRY, K., ALPERS, D.H. (1980): Jejunoileal bypass. Late metabolic sequelae and weight gain.
Am. J. Surg. 140: 347 - 350.

HANSON, W.R., OSBORNE, J.W., SHARP, J.G. (1977a): Compensation by the residual intestine after intestinal resection in the rat.
I. Influence of amount of tissue removed.
Gastroenterology, 72: 692 - 700.
HANSON, W.R., OSBORNE, J.W., SHARP, J.G. (1977B): Compensation by the residual intestine after intestinal resection in the rat.
II. Influence of postoperative time interval.
Gastroenterology, 72: 701.
HEIMBURGER, S.L., STEIGER, E., LO GERFO, P., BIEHL, A.G., WILLIAMS, M.J. (1975): Reversal of severe fatty hepatic infiltration after intestinal bypass for morbid obesity by calorie-free amino acid infusion.
Am. J. Surg. 129: 229 - 235.
HENRIKSSON, V. (1952): Nordisk Medicin, 47: 744.
HOLZBACH, R.T., WIELAND, R.G., LIEBER, C.S., DE CARLI, L.M., KOEPKE, K.R., GREEN, S.G. (1974): Hepatic lipid in morbid obesity.
New Engl. J. Med. 290: 296.
HYLAND, G., STEIN, T., WISE, L. (1977): Abnormalities of liver function following extensive jejunoileal bypass and resection in rats.
Surgery, 81: 578 - 582.
IVERSEN, B.M., SCHØNSBY, H., SKAGEN, D.W., SOLHAUG, J.H. (1976): Intestinal adaptation after jejunoileal bypass operation for massive obesity.
Europ. J. Clin. Invest. 6: 355 - 360.
JENDRASSIK, J., GROF, P. (1938): Bioch. Z. 81: 297.
JOHNSON, P.R., ZUCKER, L.M., CRUCE, J.A.F., HIRSCH, J. (1971): Cellularity of adipose depots in the genetically obese Zucker rat.
J. Lipid Res. 12: 706 - 714.
JONES, A.L., SCHMUCKER, D.L. (1977): Current concepts of liver structure as related to function.
Gastroenterology, 73: 833 - 851.
JUHL, E., QUAADE, F., BADEN, H. (1974): Weight loss in relation to the length of small intestine left in continuity after jejunoileal shunt operation for obesity.
Scand. J. Gastroenterol. 9: 219 - 221.
JUHR, N.C., UDES, H., HILLER, H.H. (1971): Modifikation der Cäcomegalie bei keimfreien Ratten.
Z. Versuchstierk. 13: 115 - 125.
JUHR, N.C. (1972): Die Cäcomegalie keimfreier Nager.
Berliner und Münchner Tierärztliche Wochenschrift, 85: 4 - 9.
KAMINSKY, D.L., JELLINEK, M., MUELLER, E.J., MENZ, L. (1975): Effect of small-intestinal bypass on hepatic lipogenesis in rats.
Surg. Forum, 26: 395 - 397.
KAMINSKY, D.L., JELLINEK, M., MUELLER, E.J. (1980): The effect of antibiotics on hepatic lipid metabolism following small bowel bypass.
J. Surg. Res. 28: 97 - 102.
VAN KAMPEN, E.J., ZIJLSTRA, W.G. (1961): Clin. Chem. Acta, 6: 538.

KAPLAN, E.L., PESKIN, G.W. (1966): Factors influencing the absorption and deposition of iron after portal systemic shunting procedures.
Surg. Forum, 17: 379 - 380.

KAUFMAN, H.J., WELDON, H.W. (1967): Intussusception, a late complication of small bowel bypass for obesity.
J. Am. Med. Assoc. 202: 1147.

KERN, W.H., HEGER, A.H., PAYNE, J.H., DE WIND, L.T. (1973): Fatty metamorphosis of the liver in morbid obesity.
Arch. Pathol., 96: 342 - 346.

KERN, W.H., PAYNE, J.H., DE WIND, L.T. (1974): Hepatic changes after small intestinal bypass for morbid obesity.
Am. J. Clin. Pathol., 61: 763 - 768.

KISSILEFF, H.R., NAKASHIMA, R.K., STUNKARD, A.J. (1979): Effects of jejunoileal bypass on meal patterns in genetically obese and lean rats.
Am. J. Physiol. 237: R217 - R224.

KOOPMAN, J.P., JANSSEN, F.G.J., VAN DRUTEN, J.A.M. (1977): Isolation of the cecal microflora of mice and comparison between the gastro-intestinal and the fecal microfloras.
Z. Versuchstierk. 19: 62 - 70.

KOOPMAN, J.P., KENNIS, H.M. (1977): Two methods to assess the gastro-intestinal transit time in mice.
Z. Versuchstierk. 19: 298 - 303.

KRAL, J.G., GØRTZ, L. (1981): in: Serono Symposium, no 28, "Obesity: Pathogenesis and Treatment" p. 255.

KREMEN, A.J., LINNER, J.H., NELSON, C.H. (1954): An experimental evaluation of nutritional importance of proximal and distal small intestine.
Ann. Surg. 140: 439.

LAMBERT,R. (1965): In: Surgery of the digestive system in the rat. p 389 - 391.
Charles C. Thomas, Springfield, Illinois, U.S.A.

LEE, F.D. (1980): In: Biopsy Pathology of the small intestine. Lee, F.D., Toner, P.G. pp 12,19-20 , 57-58, 59, 69-72.
Chapman and Hall Ltd. London.

LEWIS, L.A., TURNBULL, R.B., PAGE, T.H. (1966): Effects of jejunocolic shunt on obesity, serum lipoproteins, lipids and electrolytes.
Arch. Intern. Med. 17: 4 - 16.

LOCKWOOD, D.H., MATRUDA, J.M., MOXLEY, R.T., POZEFSKY, T., BOITNOTT, J.K. (1977): Effect of oral amino-acid supplementation on liver disease after jejunoileal bypass for morbid obesity.
Am. J. Clin. Nutr. 30: 58 - 63.

LEWIS, M.J. (1972): Lament of an unsuccessful weight watcher.
J.A.M.A. 219: 1763.

MADURA, J.A., CSICSKO, J.F., COONEY, D.R., GROSFELD, J.L. (1975): "The Fat Rat": A new experimental jejunoileal bypass model.
J. Ped. Surg. 10: 349 - 352.

MALEWIAK, M.I., GRIGLIO, S., MACKAY, S., LEMONNIER,D., ROSSELIN,G. (1977): Nutricionally induced variations in insulinaemia, blood ketone bodies and plasma and liver triglycerides in genetically obese rats.
Diabet. Metab. 3: 81 - 89.

MARESCAUX, J., STOCK, C., VASSEUR, M., RAUL, F., DOFFOEL, M., GRENIER, J.F. (1981): Imbalance in brush border enzyme activities as a possible cause of hepatic dysfunction after jejunoileal bypass in the rat.
Eur. surg. Res. 13: 427 - 437.
MARTIN,R.J., WANGSNESS, P.J., GAHAGAN,J.H. (1978): Diurnal changes in serum metabolites and hormones in lean and obese Zucker rats.
Horm. Metab. Res. 10: 187 - 192.
MARUBBIO, A.T., BUCHWALD, H., SCHWARTZ, M.Z., VARCO, R.L. (1976): Hepatic lesions of central pericellular fibrosis in morbid obesity, and after jejunoileal bypass.
AM.J. Clin. Pathol., 66: 684 - 691.
MARUBBIO, A.T., RUCKER, R.D., SCHEIDER, P.D., HORSTMANN, J.P., VARCO, R.L. BUCHWALD, H. (1979): The liver in morbid obesity and following bypass surgery for obesity.
Surg. Clin. North America, 59: 1079 - 1093.
MASON,E.E. (1981): Surgical Treatment of Obesity. p.1, p.19.
W.B. Saunders Cy, Philadelphia, London, Toronto.
MAXWELL, J.G., RICHARDS, R.C., ALBO, D. (1968): Fatty degeneration of the liver after intestinal bypass for obesity.
Am. J. Surg. 116: 648.
McCLELLAND, R.N., DE SHAZO, C.V., HEIMBACH, D.M., EIGENBRODT, E.H., DOWDY, A.B.C. (1970): Prevention of hepatic injury after jejunoileal bypass by supplemental jejunostomy feedings.
Surg. Forum, 21: 268 - 270.
McGILL, D.B., HUMPHREYS, S.R., BAGGENSTOSS, A.H., DICKSON, E.R. (1972): Cirrhosis and death after jejunoileal shunt.
Gastroenterology, 63: 872 - 877.
McGOURAN, R., RUTTER, K.R.P., ANG, L., CLEEVE, H., MAXWELL, J.D. (1978): Effect of jejunoileal bypass and equivalent resection on body weight, hepatic lipid, cytochrome P-450 and liver function in the rat.
Clin. Sci. Mol. Med. 55: 10p.
McGOURAN, R.C.M., GOLDIE, A., MAXWELL, J.D. (1979): Jejunoileal bypass in the rat: small-bowel bacteria and the effect of anti-aerobic and anti-anaerobic agents on survival and growth.
Clin. Sci. Mol. Med. 57: 27p - 28p.
MENGE,H., BLOCH, R., SCHAUMLØFFEL, E., RIECKEN, E.O. (1974): Jejunal bypass and reconstitution, in: Intestinal Adaptation, p 62.
by Dowling, R.H., Riecken, E.O. , Schattauer Verlag, Stuttgart-New York.
MEZEY,E., IMBEMBO, A.L., POTTER, J.J., RENT, K.C., LOMBARDO, R., HOLT, P.R. (1975): Endogenous ethanol production and hepatic disease following jejunoileal bypass for morbid obesity.
Am. J. Clin. Nutr. 28: 1277 - 1283.
MILLER, D.L. (1971): Rat small intestine: Development, composition and effects of perfusion.
Dig. Dis. 16-3: 247 - 254.

MOXLEY, R.T., POZEFSKY, T., LOCKWOOD, D.H. (1974): Protein nutrition and liver disease after jejunoileal bypass for morbid obesity.
New Engl. J. Med. 290: 921 - 926.

NELSON, J.L., REES, R., BONNEVAL, M.M., BORNSIDE, G.H., COHN, I. (1976): Jejunoileal bypass, liver morphology and intestinal microflora in conventional and germ-free dogs.
Surg. Forum 27, 62: 73 - 75.

NELSON, L.M., CARMICHAEL, H.A., RUSSELL, R.I., LEE, F.D. (1978): Small intestinal changes induced by an elemental diet (vivonex) in normal rats.
Clin. Sci. Mol. Med., 55: 509 - 511.

NEMETH, P.R., KWEE, D.J., WEISBRODT, N.W. (1981): Adaptation of intestinal muscle in continuity after jejunoileal bypass in the rat.
Am. J. Physiol. 241: G 259 - G 263.

NESS, PASTEWKA, PEACOCK (1964): Clin. Chem. Acta, 10: 229 - 237. Diagnostic Research Bank, National Cancer Institute Bethesda, Maryland. U.S.A.

NETTER, F.H. (1962): In: The Ciba collection of medical illustrations.
vol.3, Digestive System, part II, Lower digestive tract.
Ciba, New York.

NOLAN, J.P., VILAYAT, M. (1968): Endotoxin and the liver. Toxicity in rats with choline deficient fatty livers.
Proc. Soc. Bio. Med. 129: 29 - 31.

NYGAARD, K. (1967c): Resection of the small intestine in rats. III Morphologic changes in the intestinal tract.
Acta Chir. Scand. 133: 233 - 248.

NYGAARD, K. (1967d): Resection of small intestine in rats. IV Adaptation of gastro-intestinal motility.
Acta Chir. Scand. 133: 407 - 416.

NYGAARD, K. (1968): Nutrition and absorption after resections and bypass-operations on the small intestine in rats.
Acta Chir. Scand. 134: 63 - 77.

O'LEARY, J.P., MAHER, J.W., HOLLENBECK, J.I., WOODWARD, E.R. (1974): Pathogenesis of hepatic failure after obesity bypass.
Surg. Forum, 25: 356 - 358.

O'LEARY, J.P. (1976): An appraisal of the status of small bowel bypass in the treatment of morbid obesity.
Clin. Endocrinol. Metabol. 5: 481.

O'LEARY, J.P. (1980): Overview: jejunoileal bypass in the treatment of morbid obesity.
Am. J. Clin. Nutr. 33: 389 - 394

OTTOLENGHI,A., FACCIOLI, G., BAGGIO, E., ARMELLINI, F., BETTILI, G., BOSELLI, O. (1976): Il by-pass digiuno-ileale nel trattamento dell'obesita 'sperimentale del ratto.
Chir. Pat. Sper. 24: 155 - 162.

PAERREGAARD,A., JUSTESEN, T., PRYTZ, H., ANDERSEN, B., GUDMAND-HOEYER, E. (1982): Metronidazole treatment of bypass-enteropathy after jejunoileal shunt-operation for obesity.
Acta Chir. Scand. 148: 153 - 156.

PASSARO, E., DRENICK, E., WILSON, S.E. (1976): Bypass enteritis. A new complication of jejunoileal bypass for obesity.
Am. J. Surg. 131: 169 - 174.
PATRICIO,J., JACOTOT, B. (1977): Effect of the porto-caval shunt on the weight and cholesterolemia of normal and hyperlipidemic rats.
Biomedicine, 27: 5 - 6.
PATRICK, R.S., McGEE, J.O'D. (1980): Hepatocyte degeneration, p 22 - 23,
In: Biopsy pathology of the liver, Chapman and Hall Ltd. London.
PATRICK, R.S., McGEE, J.O'D. (1980): Normal Liver Morphology, p 4,
In: Biopsy pathology of the liver, Chapman and Hall Ltd. London.
PAYNE, J.H., DE WIND, L.T., COMMONS, R.R. (1963): Metabolic observations in patients with jejunocolic shunts.
Am.J. of Surg., 106: 273 - 289.
PAYNE, J.H., DE WIND, L.T. (1969): Surgical treatment of obesity.
Am. J. Surg. 118: 141 - 147.
PAYNE, J.H., DE WIND, L., SCHWAB, C.E., KERN, W.H. (1973): Surgical treatment of morbid obesity.
Arch. Surg. 106: 432 - 437.
PAYNE, J.H. (1980): Jejunoileal bypass for the treatment of morbid obesity.
In: Surgical Management of Obesity. p 9. Maxwell, J.D., Gazet, J-C., Pilkington, T.R.E. , Academic Press: London, Toronto, Sydney. Grune and Stratton: New York, San Francisco.
PECTOR, J.C., WINAND, J., DEHAYE, J.P., CHRISTOPHE, J. (1980): Effects of portacaval shunt and transposition on fatty acid and cholesterol biosynthesis in rat liver.
Am. J. Physiol. 239: G 83 - G 89
PECTOR, J.C., WINAND, J., DEHAYE, J.P., LECLERCQ-MEYER, V., CHRISTOPHE, J. (1981): Effects of portacaval shunt on the genetically obese Zucker rat.
Gastroentrology, 81: 932 - 937.
PETERS, P.W.J. (1972): Vergroting van het coecum bij kiemvrije knaagdieren en konijnen.
Biotechniek, 11: 229 - 236.
PETERS, R.L., GAY, T., REYNOLDS, T.B. (1975): Post-jejunal bypass hepatic disease. Its similarity to alcoholic hepatic disease.
Am. J. Clin. Pathol. 63: 318.
PHILLIPS, R.B. (1978): Small intestinal bypass for the treatment of morbid obesity.
Surg. Gynec. Obstet. 146: 455 - 468.
POULSEN, H., CHRISTOFFERSEN, P. (1979): Steatosis. p 108 and 120,
In: Atlas of Liver biopsies , Munksgaard, North and South America: J.B. Lippincott Company.
POWLEY, T.L., MORTON, S.A. (1976): Hypophysectomy and regulation of body-weight in the genetically obese Zucker rat.
Am. J. Physiol. 230: 982 - 987.

PULLAR, J.D., WEBSTER, A.J.F. (1974): Heat loss and energy retention during growth in congenitally obese and lean rats.
Brit. J. Nutr. 31: 377 - 392.

QUAADE, F. (1979): Jejunoileal bypass for morbid obesity. A bibliographic study and a randomized clinical trial.
Surg. Clin. N. Am. 59: 1055 - 1069.

RAVITCH. M.M., BROLIN, R.E. (1979): The price of weight loss by jejunoileal shunt.
Ann. Surg. 190: 382 - 391.

RICHARDSON, P.D.I., WITHRINGTON, P.G. (1981): Liver blood flow.
Gastroenterology, 81: 159 - 173.

RUTTER, K.R.P., CLEEVE, H., MAXWELL, J.D. (1978): Comparison of small intestinal bypass and equivalent small bowel resection on body weight and liver function in the Wistar rat.
Gut, 19: A454.

SACHDEV,R., ACKERMAN, N.B. (1979): Comparison of changes in intestinal length and circumference after 90 percent by-pass and 90 percent resection.
Am. J. Surg. 137: 208 - 212.

SALMON, P.A. (1971): The results of small intestine bypass operations for the treatment of obesity.
Surg. Gynec. Obstet. 132: 965 -979.

SALMON, P.A., REEDIJK, L. (1975): Fatty metamorphosis in patients with jejunoileal bypass.
Surg. Gynec. Obstet. 141: 75 - 84.

SCHONFELD, G., FELSKI, C., HOWALD, M.A. (1974): Characterization of the plasma lipoproteins of the genetically obese hyperlipoproteinemic Zucker fatty rat.
J. lipid Res. 15: 457 - 464.

SCHEDL, H.P. (1974): In: Intestinal adaptation, p 58.
Dowling, R.H., Riecken, E.O., F.K. Schattauer Verlag, Stuttgart-New york.

SCLAFANI, A., KOOPMANS, H.S., VASSELLI, J.R., REICHMAN, M. (1978): Effects of intestinal bypass surgery on appetite, food intake, and body weight in obese and lean rats.
Am. J. Physiol. 234: E389 - E398.

SCOTT, H.W., SANDSTEAD, H.H., BRILL, A.B., BURKO, H., YOUNGER, R.K. (1971): Experience with a new technic of intestinal bypass in the treatment of morbid obesity.
Ann. Surg. 174: 560.

SCOTT, H.W., DEAN, R., SHULL, H.J., ABRAM, H.S., WEBB, W., YOUNGER, R.K., BRILL, A.B. (1973): New considerations in use of jejunoileal bypass in patients with morbid obesity.
Ann. Surg. 177: 723 - 735.

SCOTT, H.W., DEAN, R.H., SHULL, H.J., GLUCK, R. (1977): Results of jejunoileal bypass in two hundred patients with morbid obesity.
Surg. Gynec. Obstet. 145: 661.

SHAGRIN, J.W., FRAM, B., DUNCAN, H. (1971: Polyarthritis in obese patients with intestinal bypass.
Ann. Internal Med.75: 377.

SHERMAN, C.D., MAY, A.G., NYE, W. (1965): Clinical and metabolic studies following bowel-bypassing for obesity.
Ann. N.Y. Acad. Sci., 131: 614 - 622.

SCHERR, H.P., NAIR, P.P., WHITE, J.J., BANWELL, J.G., LOCKWOOD, D.H. (1974): Bile acid metabolism and hepatic disease following small bowel bypass for obesity.
Am. J. Clin. Nutr. 27: 1369.

SHIBATA, H.R., MACKENZIE, J.R., LONG, R. (1967): Metabolic effects of controlled jejunocolic bypass.
Arch. Surg. 95: 413 - 428.

SIMMONS, D.J., HYLAND, G., LESKER, P.A., COHEN, M., STEIN, T., WISE, L. (1975): The effects of small-bowel resection or bypass on the rat skeleton.
Surgery, 78: 460 - 471.

SOLHAUG, J.H. (1976): Morphometric studies of the small intestine following jejunoileal shunt operation.
Scand. J. Gastroenterol. 11: 155 - 160.

TILSON, M.D., CLEVELAND, J.C., WRIGHT, H.K. (1969): A similar effect of jejunectomy on ileal mucosa in bypassed and normal ileum.
Surg. Forum, 20: 401 - 402.

TILSON, M.D. (1972): Compensatory hypertrophy of the gut.
Arch. Surg. 104: 69 - 72.

TILSON, M.D., MICHAUD, J.T., LIVSTONE, E.M. (1976): Early proliferative activity in the left colon of the rat after partial small- bowel resection.
Sur. Forum, 27: 445 - 446.

TILSON, M.D., LIVSTONE, E.M. (1980): Early proliferative activity.
Arch. Surg. 115: 1481 - 1485.

TOULOUKIAN, R.J., SPENCER, R.P. (1971): Blood flow to the ileal remnant following massive intestinal resection.
Surg. Forum 22: 370 - 371.

TOULOUKIAN, R.J., SPENCER, R.P. (1972): Ileal blood flow preceding compensatory hypertrophy.
Ann. Surg. 175: 320 - 325.

TRIER, J.S. (1978): Anatomy of the small intestine, in: Gastro-intestinal disease.
Sleisenger, M.H. Fordtran, J.S., 2nd Edition, p 980, Saunders, Philadelphia, U.S.A.

TUMA, D.J., VANDERHOOF, J.A., SORRELL, M.F. (1978): Impaired hepatic drug metabolism after jejunoileal bypass in rats.
J. Pharmacol. Exp. Ther. 206: 167 - 171.

VANDERHOOF, J.A., TUMA, D.J., SORRELL, M.F. (1979): Role of defunctionalized bowel in jejunoileal bypass-induced liver disease in rats.
Dig. Dis. Sci., 24: 916 - 920.

VANDERHOOF, J.A., METZ, M.J., TUMA, D.J., ANTONSON, D.L., SORRELL, M.F. (1980): Effect of improved absorption on development of jejunoileal bypass-induced liver dysfunction in rats.
Dig. Dis. Sci., 25: 581 - 586.

VAN ITALLIE, T.B. (1980): "Morbid" obesity: a hazardous disorder that resists conservative treatment.
Am. J. Clin. Nutr. 33: 358 - 363.

DE WAARD, H. (1978): In: Effects on lipid and glucose metabolism of diets with different types of fat and sugar in male fatty Zucker rats. pp 8,9,25,34.
NIZO, Ede, Holland.

WAHLEFELD, A.W. (1974): Triglycerides. Determination after Enzymatic Hydrolysis.
In: H.U.Bergmeyer, ed. Methods of enzymatic analysis, p 1831, 2nd English ed. Verlag Chemie Weinheim and Academic Press, Inc., New York and London.
WILLIAMSON, R.C.N. (1978a): Intestinal adaptation 1.
New Engl. J. Med. 298: 1393 - 1402.
WILLIAMSON, R.C.N. (1978b): Intestinal adaptation 2.
New Engl. J. Med. 298: 1444 - 1450.
DE WIND, L.T., PAYNE, J.H. (1976): Intestinal bypass surgery for morbid obesity. Long-Term results.
J.A.M.A., 236: 2298 - 2301.
WOOD, L.C., CHREMOS, A.N. (1963): Treating obesity by "short-circuiting" the small intestine.
J.A.M.A. 186: 169.
YOST, R.L., DUERSON, M.C., RUSSELL, W.L., O'LEARY, J.P. (1979): Doxycycline in the prevention of hepatic dysfunction; an evaluation of its use following jejunoileal bypass in humans.
Arch. Surg. 144: 931 - 934.
YOUNOSZAI, M.K., ADEDOYIN, M., RANSHAW, J. (1978): Dietary components and gastrointestinal growth in rats.
J. Nutr. 108: 341 - 350.
ZUCKER, L.M., ZUCKER, T.F. (1961): Fatty, a new mutation in the rat.
J. Hered. 52: 275 - 278.
ZUCKER, T.F., ZUCKER, L.M. (1962): Hereditary obesity in the rat associated with high serum fat and cholesterol.
Proc. Soc. Exp. Biol. Med. 110: 165 - 171.
ZUCKER, T.F., ZUCKER, L.M. (1963): Fat accretion and growth in the rat.
J. Nutr. 80: 6 - 19.
ZUCKER, L.M. (1965): Hereditary obesity in the rat associated with hyperlipemia.
Ann. N.Y. Sci. 131: 447 - 458.
ZUCKER, L.M. (1967): Some effects of caloric restriction and deprivation on the obese hyperlipemic rat.
J. Nutr. 91: 247 - 254.
ZUCKER, L.M. (1972): Fat mobilization in vitro and in vivo in the genetically obese Zucker rat "fatty".
J. Lipid Res. 13: 234 - 243.

DANKBETUIGING

Een proefschrift is niet het werk van één persoon doch komt tot stand dank zij de medewerking van velen. Een ieder die zijn medewerking direct of indirect heeft verleend wil ik gaarne bedanken. De reglementen staan het niet toe om alle medewerkers persoonlijk te bedanken. Echter enkele woorden van dank tot de belangrijkste medewerkers lijken mij zeker op zijn plaats.

De medewerkers van afdeling IV van het Centraal Dierenlaboratorium (hoofd: Dr. W.J.I. v.d. Gulden), met name de heer J. Koedam, Mw. E.J.J. v.d. Vorle - Houben en de heer W. M. Smits hebben zich op bijzondere wijze ingezet evenals Mw. H.M. Kennis, die alle kweken en "passage-tijden" verzorgde.
Drs. T. Manschot heeft met grote nauwkeurigheid de vele histologische preparaten beoordeeld, geruggesteund door Prof. Dr. U.J.G. van Haelst.
Mede dankzij de medewerkers van het Klinisch Chemisch Laboratorium (hoofd: Dr. P.J.J. van Munster) is hoofdstuk 5 tot stand gekomen.
Dr. C.H.J. Stockmann van de afdeling heelkunde en dr. J.B.M.J. Trimbos van de afdeling inwendige geneeskunde van het St. Franciscus Gasthuis in Rotterdam stelden op een bijzonder coöperatieve wijze de gegevens ter beschikking van de in het verleden door Prof. Dr. H.H.M. de Boer aldaar geopereerde patiënten.
De ontelbare getallen van dit onderzoek werden statistisch tot de orde geroepen door Dr. R. de Graaf met medewerking van ir. J. Mulder van de Mathematische Statistische Adviesafdeling (hoofd: Drs. P. van Elteren).
De medewerkers van de medische bibliotheek (hoofd: de heer E. de Graaff) droegen, al dan niet met computerassistentie, altijd bereidwillig bij tot het verzamelen van de literatuur.
De bewerking hiervan lag voor een groot deel in handen van drs. J. Heevel.
Over het fotografisch gedeelte van dit proefschrift liet de heer C.A. de Bruin van de afdeling Medische Fotografie (hoofd: de heer A.Th.A.J. Reynen) op flitsende wijze zijn licht schijnen.
Het manuscript werd met argusogen bekeken op inhoud en Engels door dr. Thijs Hendriks en drs. Jan van Uem.
Leo Hendriks wist mijn gedachten over de voorpagina in tekening om te zetten.
Dankzij drs. Ad v.d. Kley en de inzet van Trees en Arie v.d. Kley kon de tekstverwerking op geavanceerde wijze geschieden.
Last but not least is Hester mij tot grote steun geweest. Bovendien heeft zij het typewerk van de eerste tot de laatste letter verzorgd.

CURRICULUM VITAE

De auteur van dit proefschrift werd op 7 december 1945 te Heerlerheide (Heerlen) geboren. Het lager onderwijs genoot hij te Heerlerheide. Hij bezocht het St. Bernardinus-college te Heerlen en behaalde het einddiploma gymnasium-B in 1965. Vervolgens studeerde hij geneeskunde aan de Katholieke Universiteit te Nijmegen. In 1973 legde hij aldaar het artsexamen af. Ter voorbereiding op de tropen was hij vervolgens een jaar werkzaam als algemeen assistent in het St. Joseph Ziekenhuis te Veghel. Na de tropencursus en enkele waarnemingen in de huisartsenpraktijk vertrok hij in 1974 naar het St. Joseph Hospital te Kilgoris, gelegen in het gebied der Maasai, in Kenya. Tot eind 1976 was hij hier werkzaam als algemeen arts en medisch directeur in dit missie-ziekenhuis.
Op 1 januari 1977 begon hij met de opleiding algemene heelkunde aan de universiteit van Nijmegen (opleider Prof. Dr. W.J.H. Schmidt en later Prof. Dr. H.H.M. de Boer), welke opleiding per 1 januari 1983 voltooid zal zijn.

S T E L L I N G E N

behorende bij het proefschrift

J E J U N O I L E A L   B Y P A S S

An experimental study in Zucker rats
and a retrospective study of morbidly obese patients

In het openbaar te verdedigen
op donderdag 18 november 1982
des namiddags te 4 uur

door

J.E.L. CREMERS

De hamvraag van dit onderzoek is hoeveel dunne darm bij de dikke rat te behouden om voldoende vet kwijt te raken.

**

De grootste invloed op het gewichtsverlies na een "jejunoileal bypass" wordt waarschijnlijk geleverd door de lengte van het functionerende stuk dunne darm.

**

Adaptatie van de dunne darm na uitgebreide resecties of kortsluitingsoperaties van de dunne darm bestaat op zijn minst uit twee verschillende en na elkaar optredende mechanismen: toename van de dikte van de darmwand en vervolgens toename van de lengte en de omtrek van de dunne darm.

**

Bij patiënten met morbide adipositas is, evenals bij vette Zucker ratten, de dunne darm gemiddeld langer dan bij soortgenoten met een normaal gewicht.

**

Naast ondervoeding en naast vrijkomen van toxines uit het uitgeschakelde stuk dunne darm na een "jejunoileal bypass" dient ook vermindering van bloedtoevoer naar de lever via de vena portae beschouwd te worden als mogelijk leidend tot leverinsufficiëntie.

**

Bij de vette Zucker rat dient het aanbeveling een operatiemicroscoop te gebruiken voor het leggen van darmnaden.

**

Late recidiefbloedingen uit varices van slokdarm of maag na aanleg van een distale splenorenale shunt volgens Warren kunnen berusten op ontwikkeling van (nieuwe) collaterale venen met hepatofugale flow.

**

De infrarood-contact-coagulatie is een aanwinst bij het behandelen van letsels van parenchymateuze organen zoals lever en milt.

**

Gezien het belang van de totale mobilisatie van het rectum in de behandeling van de rectumprolaps is het aannemelijk, dat de bekkenbodemplastiek volgens Roscoe Graham - Goligher slechts dezelfde betekenis heeft als de procedures die het rectum aan het sacrum fixeren.

**

De behandeling van een subcutane Achillespees ruptuur volgens Weber, bestaande uit primaire hechting en vroeg-functionele nabehandeling, is comfortabel voor de patiënt en leidt tot goede resultaten.

**

De cephalosporinen van de derde generatie betekenen een aanwinst voor de behandeling van infecties veroorzaakt door gram-negatieve micro-organismen.

**

De opvatting in de moderne studies over griekse architectuur, dat er bij antieke gebouwen slechts drie "voet"-maateenheden, nl. de Dorische (32,8 cm), de Ionisch-Attische (29,6 cm) en de Samische (35 cm) gangbaar waren, is in strijd met de antieke bronnen.

**

In de twintigste eeuw is de grootste bijdrage aan de presentatie van de klassieke gitaar en aan uitbreiding van het repertoire voor gitaar geleverd door de autodidact Andrés Segovia.

**

Gezien 's lands precaire financiële situatie lijkt het niet verantwoord tot de aanschaf van nieuwe (kern)wapenen over te gaan voordat het huidige materieel verbruikt is.

**

De lasten des overvloeds kunnen niet pregnanter worden weergegeven dan door de weeklacht van Marion Lewis:

"My intertriginosity
Is caused by adiposity;
I wonder where the increment will end?

Such fleshly generosity
Impedes my true velocity
And also makes it difficult to bend.

I have no curiosity
To be a great monstrosity-
Such wishfulness I cannot comprehend;

In fact, this corporosity
Fills me with animosity,
Because I can't reverse the "growing" trend!"

J.A.M.A. (1972), 219: 1763.

**